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Synthesis of 1-Aryl-3-Pyrazolidinones through 3-(2'-Arylaminoethyl)-1,4,2-Dioxide-5-one intermediates

David G. Lincoln

SYNTHESIS OF 1-ARYL-3-PYRAZOLIDINONES THROUGH 3-(2'-ARYLAMINOETHYL)-1,4,2-DIOXAZOL-5-ONE INTERMEDIATES

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MAY, 1983

THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE

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APPROVED:

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TABLE OF CONTENTS

Page

ABSTRACT.....ii

ACKNOWLEDGEMENTS.....iii

LIST OF TABLES.....iv

HISTORY.....1

INTRODUCTION.....5

RESULTS.....16

DISCUSSION.....35

EXPERIMENTAL.....46

REFERENCES.....61

ABSTRACT

A new preparation of 1-arylpyrazolidinones, not involving the prior preparation of arylhydrazines, is reported. The reaction of 3-arylaminopropiono hydroxamic acids with chloroformates gives the title compounds. This transformation is discussed in terms of the intermediacy of the corresponding 1,4,2-dioxazol-5-one ring system. These intermediates undergo mild nitrogen-atom induced decomposition with simultaneous N-N bond formation. The effects of chloroformates and aryl substitution is discussed.

ACKNOWLEDGEMENTS

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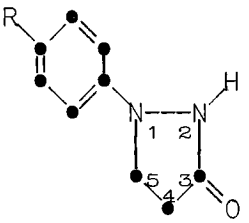
LIST OF TABLES

			PAGE
TABLE I	-	Yields and Properties of Arylsubstituted-3-propionates from Michael Addition Reactions	19
TABLE II	-	Yields and Properties of Arylsubstituted Hydroxamic Acids	23
TABLE III	-	Yields of Pyrazolidinone 1 (R=H) and Imidazolidinone 32 (R=H) Using Various Chloroformates in the Hydroxamic Acid to Pyrazolidinone Reaction	27
TABLE IV	-	Yields and Properties of Substituted Pyrazolidinones 1 and Imidazolidinones 32 from Reaction of Hydroxamic Acids 76 with Trichloroethyl Chloroformate	29

HISTORY

1-Aryl-3-pyrazolidinone is the accepted name given by Chemical Abstracts to oxo-derivatives of pyrazole. The pyrazolidinone ring system is not aromatic; however, oxidation results in the aromatic compound 1-aryl-3-hydroxy-pyrazole (2).



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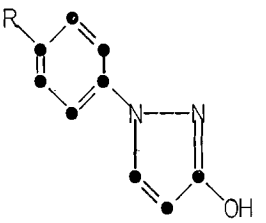


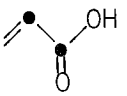
2

These compounds are monoacidic bases forming weak salts[1], and their reactivity can be compared to aliphatic hydrazides. Hydrolysis by acid or base destroys the pyrazolidinone ring system.

Extensive work has been done on the pyrazolidinones, due mainly to their application in photography as silver halide developers. Specifically, 1-phenyl-3-pyrazolidinone or Phenidone has been used widely in the photographic industry since 1940[2].

Traditional syntheses for 1 and its derivatives include reactions of α,β-unsaturated acids 3, α,β-unsaturated esters 4, α,β-unsaturated amides 5, and 3-bromopropionates 6 with aryl hydrazines 7[3]. However, the isomeric 2-aryl-3-pyrazolidinone 8 can be isolated as well with 3, 4, or 5 as starting materials.

Scheme 1



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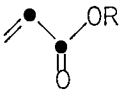
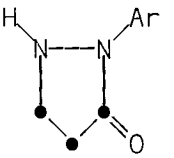


4

+ NH_2NHAr ⟶ 1 +



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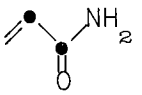

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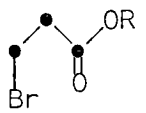

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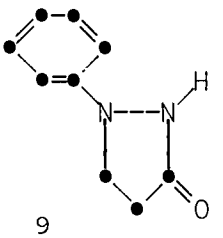
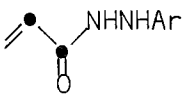
The most common approach to Phenidone involves the reaction of α,β-unsaturated esters with phenylhydrazine in the presence of sodium ethoxide or sodium methoxide to give predominately the 1-isomer 9[4].



9

Cyclization of α,β-unsaturated acid hydrazides[5] as well as cyclization of β-hydrazino acids under acidic conditions also result in pyrazolidinones[6].



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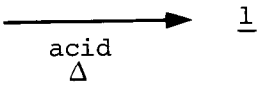
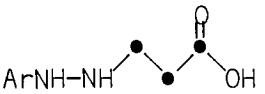
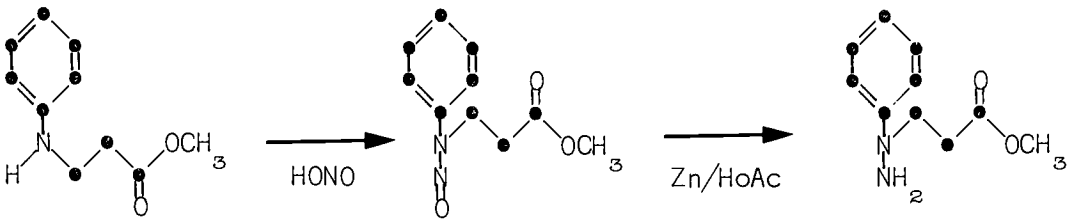


1

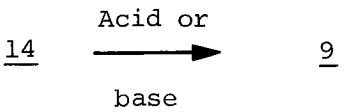


11

More recently, Simonova developed a synthesis of Phenidone which utilized β-N-phenylalanine methyl ester 12. Nitrosation of 12 gave N-nitroso derivative 13 which after Zn reduction yielded the β-hydrazino ester 14. Cyclization of 14 gave 9 in 25% yield[7].



12 13 14

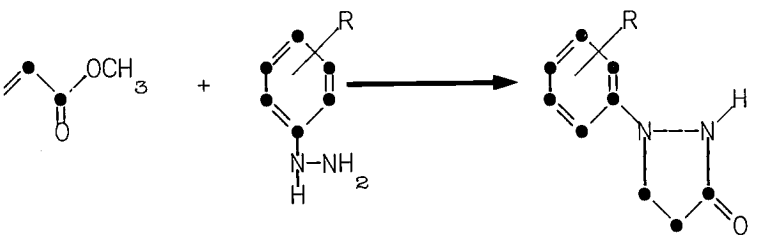


14 9

All of the above methods rely on arylhydrazine precursors in the synthesis of the pyrazolidinone ring system. This work deals with synthetic alternatives for the desired class of compounds which do not use hydrazines.

INTRODUCTION

The use of arylhydrazines in the synthesis of pyrazolidinones has been reviewed in the history chapter. This approach is restrictive in the sense that arylhydrazines with electron-donating or strongly electron-withdrawing substituents are sometimes difficult to prepare in good yield[8]. Arylhydrazines are often derived from reduction of the corresponding diazonium compound 18, and these diazoniums with strong electron-withdrawing or electron-donating substituents are often unstable.

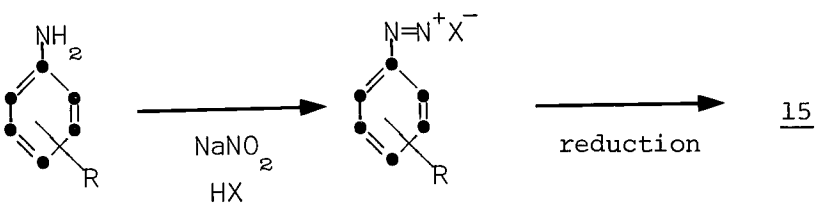


4 15 16

R = electron-withdrawing

or

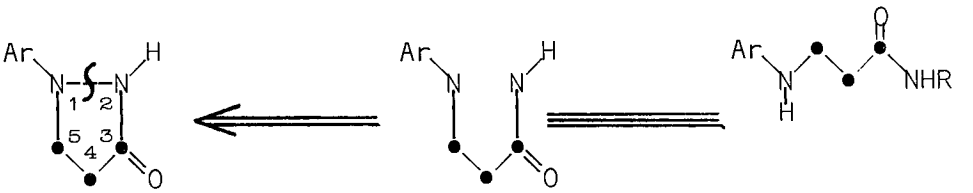
electron donating



17 18

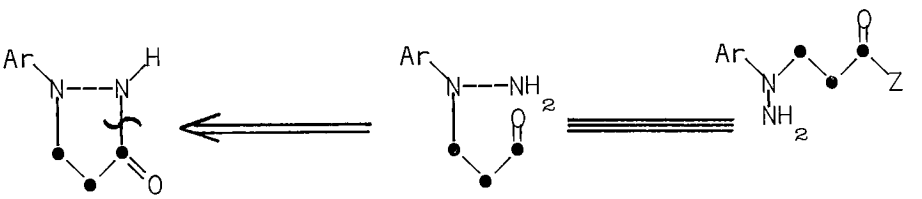
A strategy to prepare the desired heterocyclic ring system 1 without the use of arylhydrazine precursors was derived by retrosynthetic analysis.

CASE 1 (1-2 bond cleavage)



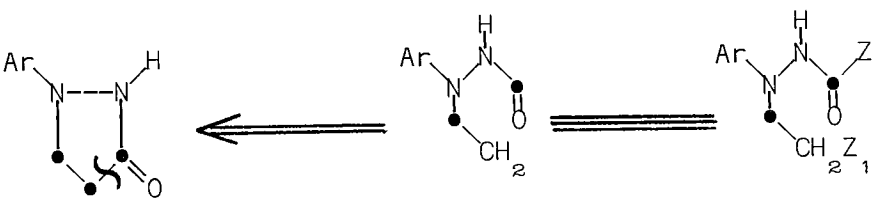
1 19 20

CASE 2 (2-3 bond cleavage)



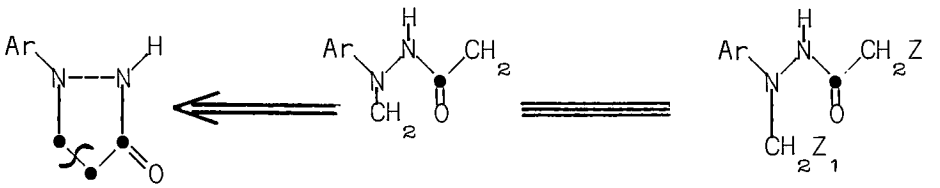
1 21 22

CASE 3 (3-4 bond cleavage)



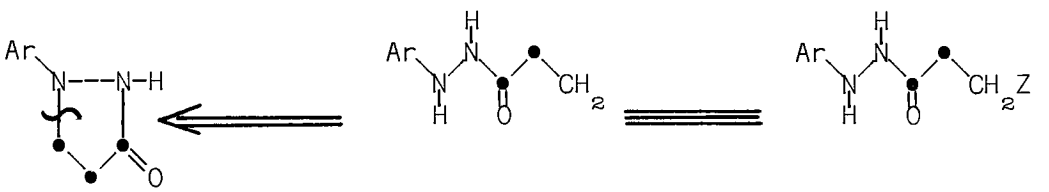
1 23 24

CASE 4 (4-5 bond cleavage)



1 25 26

CASE 5 (1-5 bond cleavage)

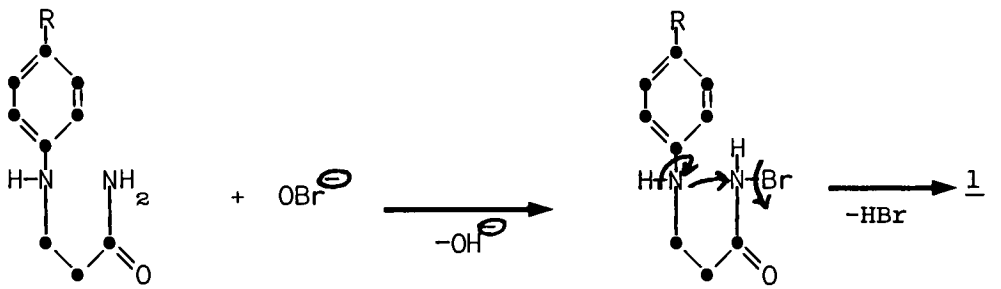


1 27 28

Case 2 represents the traditional synthesis of 1 through β-hydrazino intermediates. Cases 3,4, and 5 result in hydrazide intermediates, necessitating the use of mono- and di-substituted hydrazine precursors. Ring cyclization using intermediates 24 and 26 could be envisioned using either carbanion or organometallic chemistry. Cyclization of intermediates 28 (Z = halogen) are known to be low yielding[9].

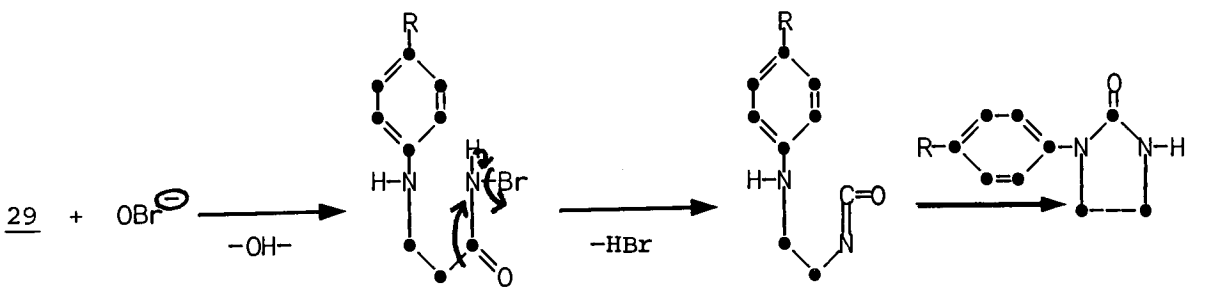
Since our goal was to eliminate arylhydrazines, we felt the best approach would be N-N bond formation in the final cyclization step (Case 1). Case 1 utilizes an amide intermediate 20, and we reasoned that an electrophilic amide nitrogen would be necessary for the formation of the nitrogen-nitrogen bond. A N-bromoamide, 30, a

reactive intermediate in the Hofmann Rearrangement, might be expected to fulfill this requirement. Thus, nucleophilic displacement of bromide at the amide nitrogen by the anilino nitrogen in 30 would give rise to the desired ring system 1 as shown below.



29 30

However, alkyl migration could also result (Hofmann Rearrangement) and the imidazolidinone 32 would result via the intermediate isocyanate 31.

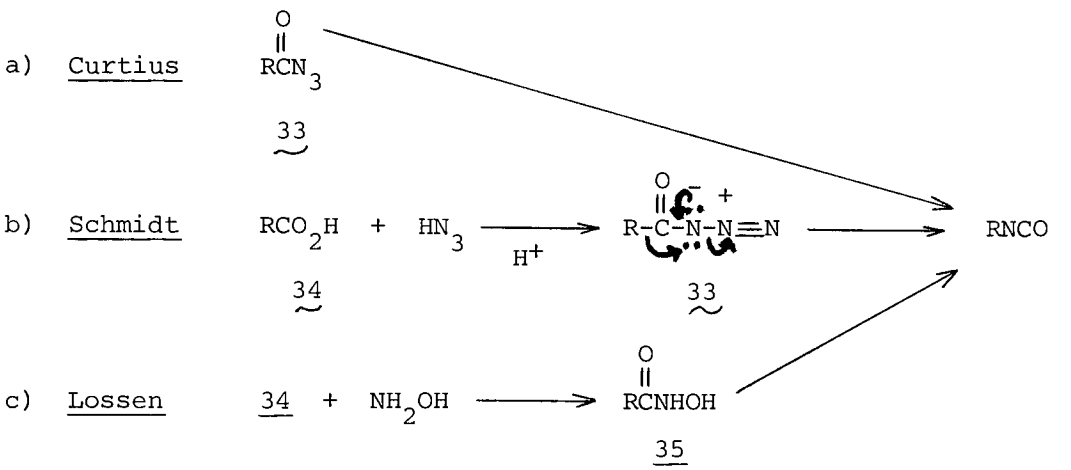


30 31 32

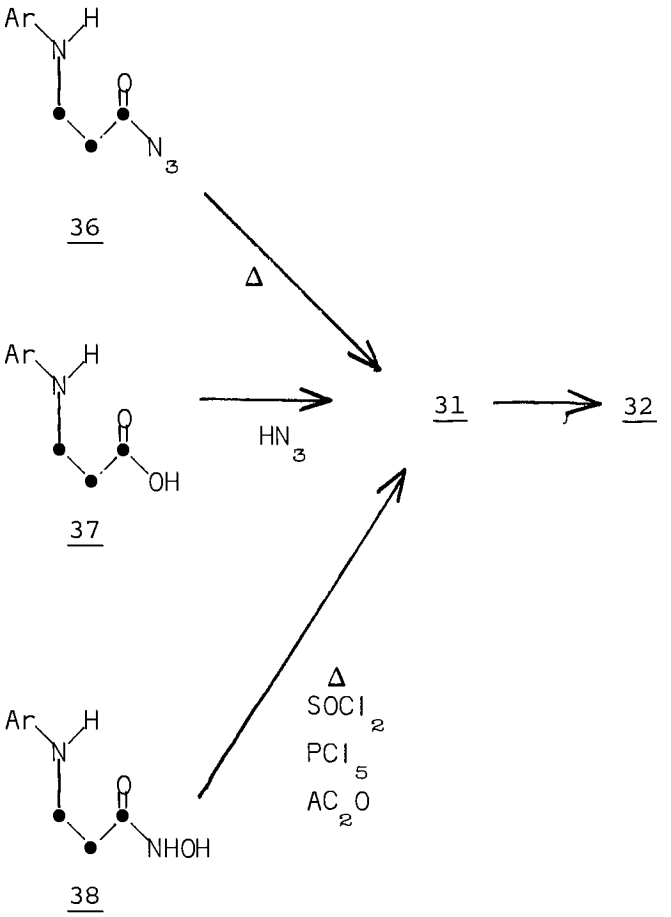
Literature precedent seemed to favor the second rearrangement via the Hofmann reaction[10].

Reactions in which migration to amide nitrogen (i.e. Curtius, Schmidt, and Lossen) is important were considered in context to the proposed study. These reactions result in isocyanates 34 as products

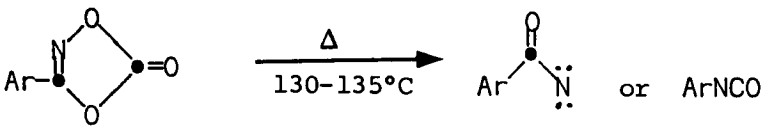
and are generally considered to be concerted rearrangements. Discrete acylnitrenes are typically not found as reactive intermediates in these isocyanate-forming reactions[11].



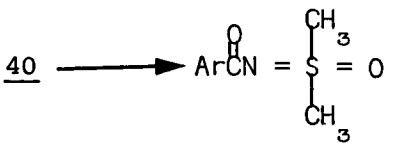
As with the Hofmann rearrangement, we feared concerted isocyanate formation might be more favorable than the desired N-N bond forming reaction in the decomposition of 36, 37, and 38.



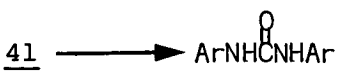
We knew the 1,4,2-dioxazol-5-one ring system had been used to generate isocyanates in a manner similar to the Curtius rearrangement[12]. Thermolysis or photolysis of these compounds leads to isocyanate or isocyanate-derived products important to the polyurethane industry[13]. Upon closer examination, we found that Sauer et al. had investigated the thermolysis and photolysis of various substituted 3-aryl-1,4,2-dioxazol-5-one derivatives[14]. These workers demonstrated that in addition to isocyanate-derived products, intermolecular addition products, presumably arising from a reactive acylnitrene 40, were obtained.



39 40 41



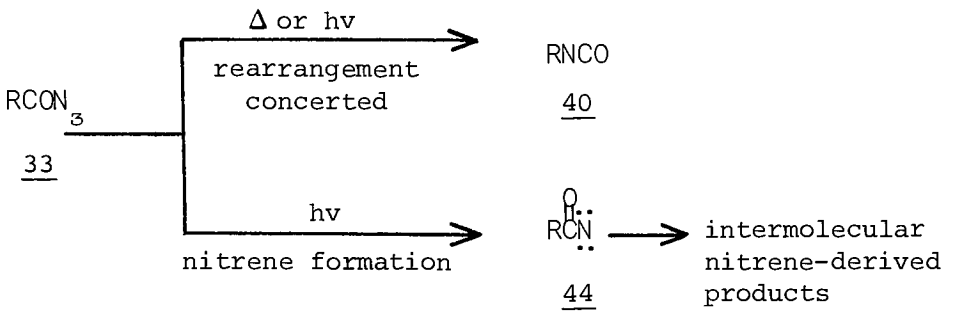
42



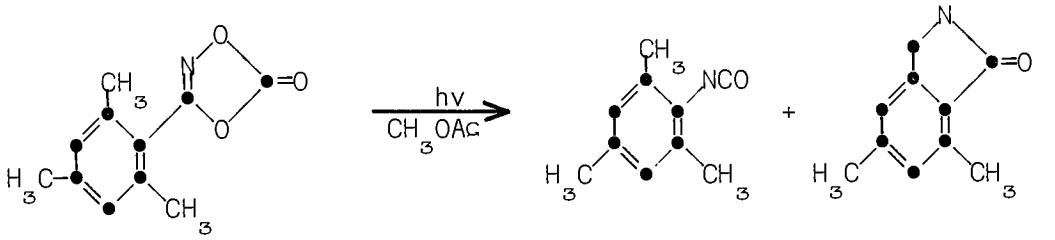
43

The intermolecular nitrene addition product, N-acylsolfoxoimine 42, was obtained by thermolysis of 39 in the presence of DMSO and was considered a result of nucleophilic attack of DMSO on the electron-deficient acylnitrene. The study showed varying amounts of isocyanate-derived ureas and addition products depending on the nature of the ring substituent. This work along with a later study involving the photolysis of acylazides suggested the intermediacy of a common acylnitrene at least for the intermolecular addition reaction[15].

Evidence for acylnitrenes from thermolysis of acylazides has been discounted by Lwowski[16]. Isocyanate yields were independent of nitrene-derived products when the reaction was carried out in the presence of nitrene traps. Photolysis of acylazides, on the other hand, has been found to lead to acylnitrenes; although these apparently are not involved in the isocyanate rearrangement.

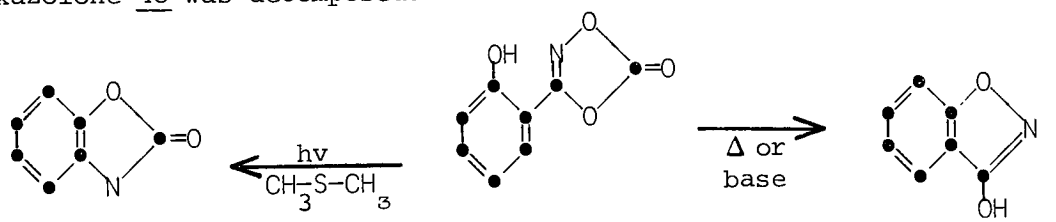


Intramolecular bond formation by capture of a reactive acylnitrene was also found by Sauer[12]. Decomposition of the dioxazolone 45 resulted in isocyanate 46 and the isoindolinone 47.



45 46 47

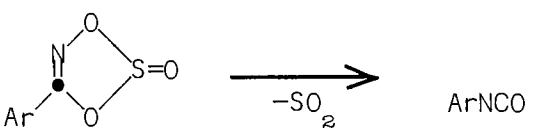
Formation of 47 probably results by insertion of the acylnitrene into a C-H bond of the methyl group. Intramolecular oxygen-nitrogen bond formation was also observed when the salicylic acid-derived dioxazolone 48 was decomposed.



49 48 50

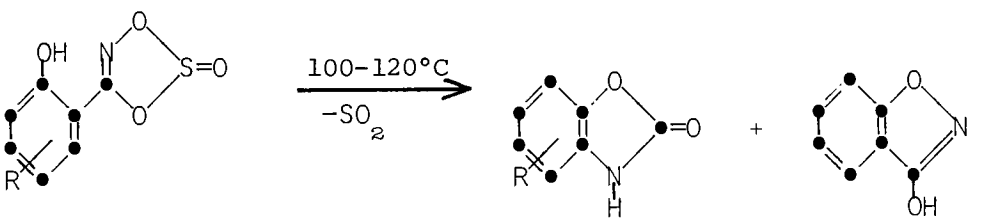
Benzoxazolone 49, the isocyanate-derived product, was obtained from the photolysis of 48 in dimethylsulfide. Thermolysis or treatment of 48 with base gave the benzisoxazolone 50, representative of O-N bond formation.

A class of heterocyclic analogs of dioxazolones is the 1,3,2,4-dioxathiazol-s-oxide 51 derived from hydroxamic acids and thionyl chlorides under mild conditions[17]. These compounds are also known to give isocyanates with loss of SO_2 by thermolysis[18].

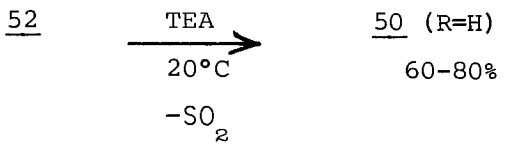


51 41

The sulfur analog of 48, 3-(2-hydroxyphenyl)-1,3,2,4-dioxathiazol-S-oxide, 52 (R=H), was found to give a mixture of benzoxazolone 49 (R=H) and benzisoxazolone 50 (R=H) upon thermolysis. Treatment with base at low temperatures gave almost exclusively the product 50, characteristic of O-N bond formation[19].

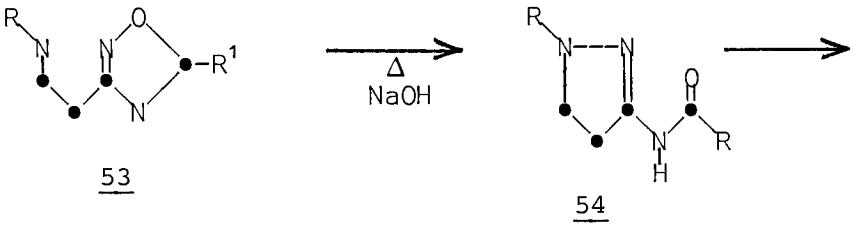


52 49 (R=H) 50% 50 (R=H) 50%

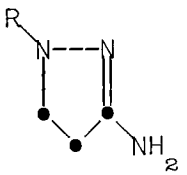


One disadvantage to using compounds of type 51 is their reported hydrolytic instability[20].

Based on the known chemistry of dioxazolones, especially the intramolecular cyclization reactions already described, we felt appropriately substituted dioxazolone precursors could decompose to pyrazolidinones of type 1 by nitrogen-nitrogen bond formation. In addition, a recent report discussing rearrangement of 1,2,4-oxadiazoles 53 to 3-amino-pyrazolines 55 encouraged us further[21].

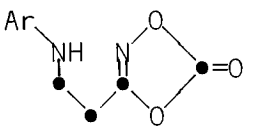


53 54



55

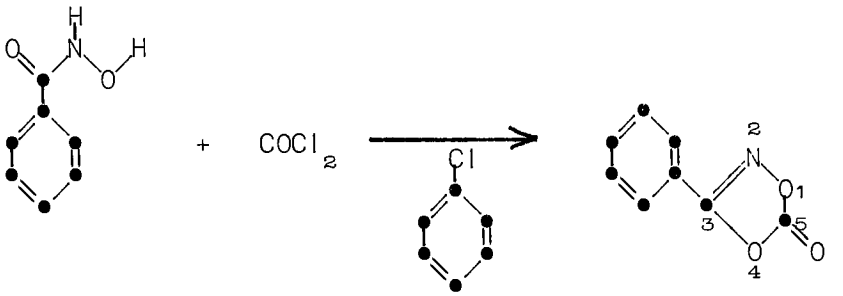
The necessary dioxazolones pertinent to our study would be 3-(β-arylaminoethyl)-1,4,2-dioxazol-5-ones 56 prepared from the corresponding hydroxamic acids. This report deals with the preparation of 56 and their rearrangement to the desired pyrazolidinones 1 and imidazolinones 32.



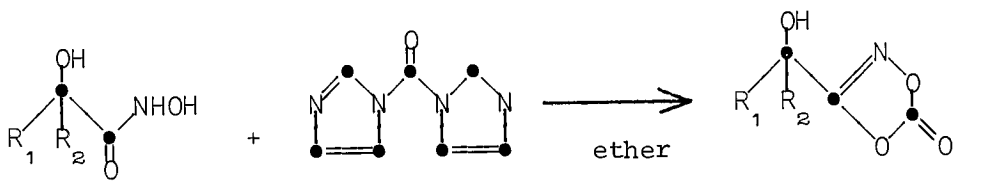
56

RESULTS

Preparation of the 1,4,2-dioxazol-5-one ring system was first reported by Beck in 1951[22]. Treatment of the hydroxamic acid 57 with phosgene 58 resulted in an 85% yield of dioxazolone 59. These compounds are prone to hydrolysis converting back to starting hydroxamic acid. Other approaches to dioxazolones include the use of a phosgene alternative such as carbonyldiimidazole 61[23].

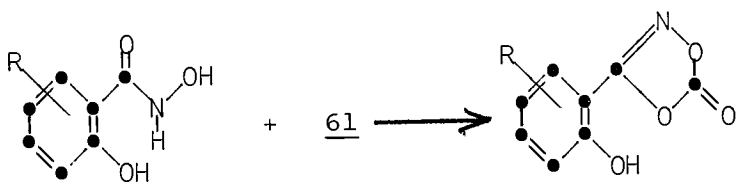


57 58 59



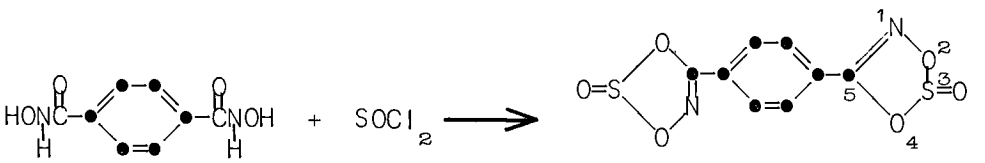
60 61 62 91%

$R_1 = R_2 = C_6H_5$



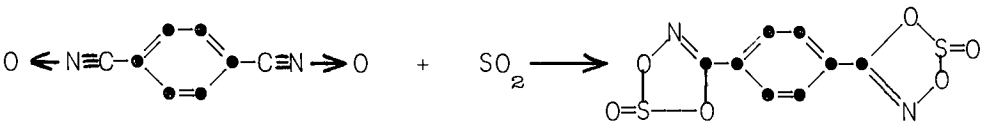
63 64

An analogous ring system, 1,3,2,4-dioxathiazol-S-oxide, e.g. 65, can be generated by the reaction of thionyl chloride 66 and hydroxamic acids[24]. The reaction of the dinitrile-oxide 68 with SO_2 also resulted in the same compound[25].



67 66 65

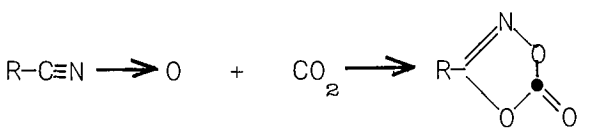
96%



68 69 65

86%

The similar cycloaddition reaction of nitrile oxides 70 with carbon dioxide, i.e. 70 + 71 → 72, has apparently not been reported.

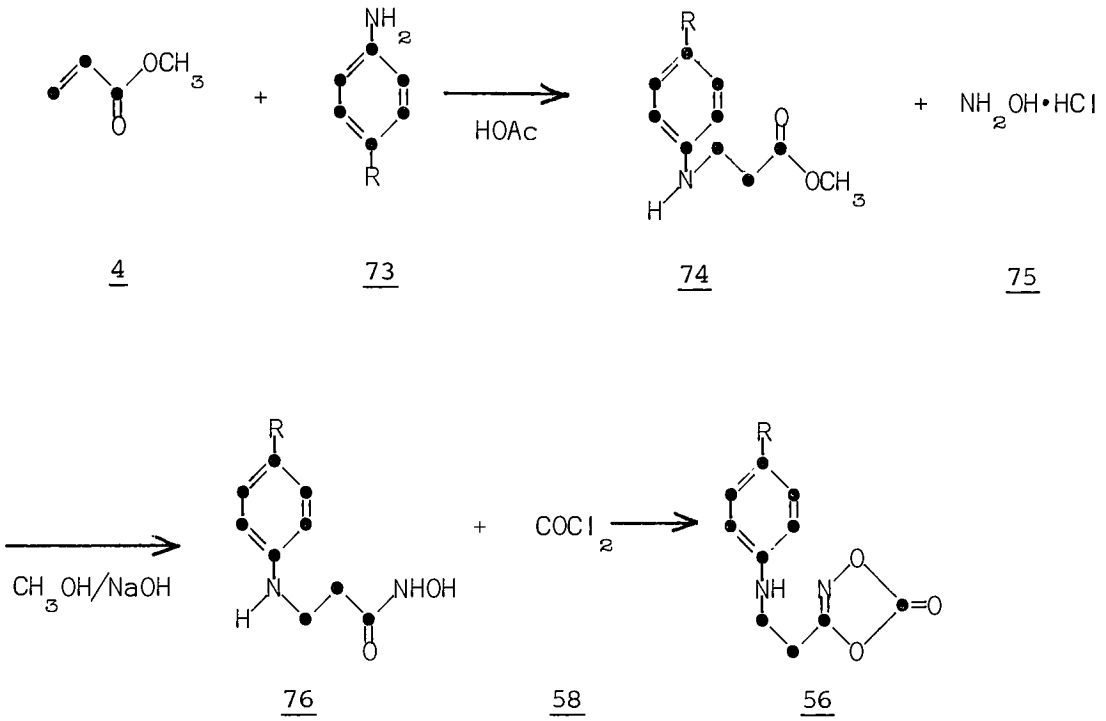


70 71 72

Although the reaction of 70 with ketones has been reported to yield substituted 1,4,2-dioxazoles in low to moderate yields[26].

Since our goal was the dioxazolone intermediate 56, we reasoned that reaction of the substituted hydroxamic acid 76 and phosgene 58 would result in the targeted dioxazolone (Scheme 2).

Scheme 2



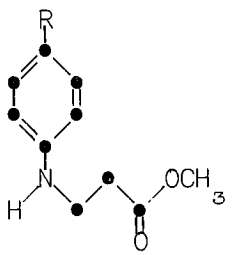
4 73 74 75

76 58 56

The substituted hydroxamic acid 76 (R=H) could be derived through the known 3-anilinopropionates 74 (R=H). Michael reaction of aniline 73 (R=H) with methyl acrylate under acidic conditions gave a 79% yield of 74 (R=H)[27]. A series of arylsubstituted-3-anilinopropionates were synthesized along with the unsubstituted case, using similar conditions. Results of these reactions are shown in Table I.

TABLE I

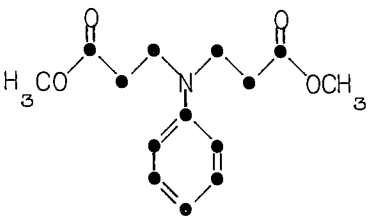
Yields and Properties
of Arylsubstituted-3-propionates
from Michael Addition Reactions



74

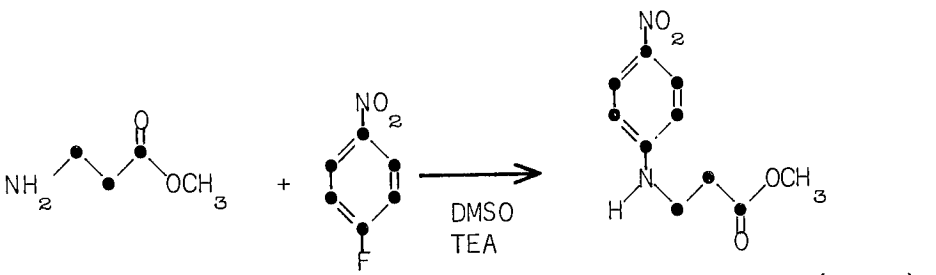
R	% Yield	B.P. °C (mm)	M.P. °C
CH_3	46	144-145(0.35-0.5)145-146(5-6 mm)[27]	
OCH_3	81	146-170(0.5-1.5)143-152(0.65)[28]	
Cl	61		52-54(58-60)[29]
H	79	110-130(0.7-1.5)139-146(1-2)[27]	

No difficulties were encountered in generating these propionates except for 74 (R=CH_3). In this example the di-Michael addition product 77 was isolated. Literature-cited conditions, $SnCl_4$-Toluene, minimized the occurrence of this product[27].



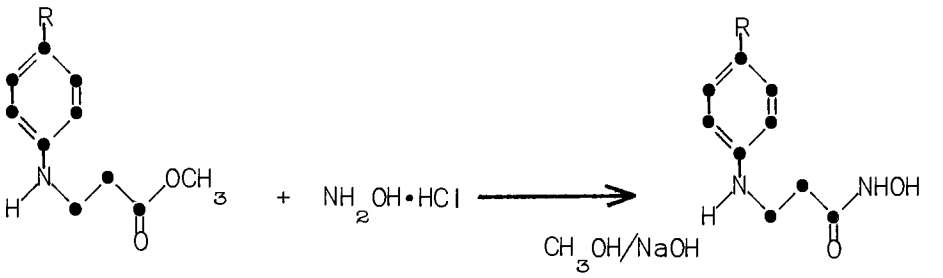
77

The propionate intermediates 74 (R=H, CH_3, OCH_3) were low-melting solids and purification required distillation. When the substitution involved R=Cl or R=NO_2, higher melting solids were obtained and these compounds were purified through crystallization. The corresponding 74 (R=NO_2) derivative was prepared from a different route due to the lack of reactivity of p-nitroaniline towards Michael addition with methyl acrylate[30]. The reaction of 4-nitrofluorobenzene (79) with methyl 3-amino-propionate (78) in DMSO resulted in good yields of 74 (R=NO_2).



78 79 74

The respective hydroxamic acids 76 were unknown. However, general conditions for conversion of esters to hydroxamic acids were successfully applied[31].



74 75 76

Treatment of the esters 74 with hydroxylamine-hydrochloride 75 resulted in reasonable yields of the hydroxamic acids as shown in Table II.

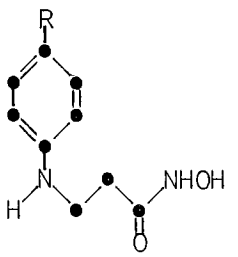
The progress of reaction could be monitored by IR (disappearance of C=O band at 1725 cm^{-1} and the formation of the $-\overset{O}{\overset{\|}{C}}NHOH$ band at 1630 cm^{-1}) as well as TLC. Reactions times varied 1-2 hours at room temperature, and, with R=NO_2, mild heat was applied to complete the reaction.

Since the conversion to hydroxamic acid was done under basic conditions, acidification of the reaction mixture prior to isolation was necessary to isolate the neutral compound. When the reaction was neutralized with concentrated HCl, only one equivalent of the acid was added, otherwise the hydrochloride salt of 76 was obtained. In one case, R=Cl, the hydrochloride salt was isolated because attempts to isolate the neutral hydroxamic acid resulted only in impure oils.

With completion of the synthesis of the hydroxamic acid intermediate, we were now ready to attempt the preparation of the requisite dioxazolone by reaction with phosgene in the presence of triethylamine (TEA). It was rationalized that reaction of phosgene with the hydroxamic acid in the presence of TEA would result predominately in the desired dioxazolone 56, due to the greater acidity of the hydroxamic acid ($RC(=O)NHOH$) functionality versus the anilino N-H. Addition of an equivalent amount of phosgene at low temperatures resulted in incomplete reaction as evidence by TLC analysis. When the reaction was allowed to warm to room temperature, TLC analysis indicated a multi-component reaction mixture. None of the desired dioxazolone could be isolated using these conditions. Excess phosgene was added to 76 (R=H) at slightly higher temperatures; a 41% yield of the N-phenyl-N-chlorocarbonyldioxazolone 80 was obtained. The isolated dioxazolone 80 exhibited spectral properties consistent with the proposed structure. Significantly, a double C=O stretching band was observed in the infrared spectrum at 1825 cm^{-1} and 1865 cm^{-1}. Sauer describes this double band between 1825 cm^{-1} and 1875 cm^{-1} as being characteristic of the dioxazolone ring[12]. The compound 80, also characterized by its ^{1}H NMR and mass (21% parent ion, base ion CO_2) spectra, was stable at room temperature (MP 67°-68°C).

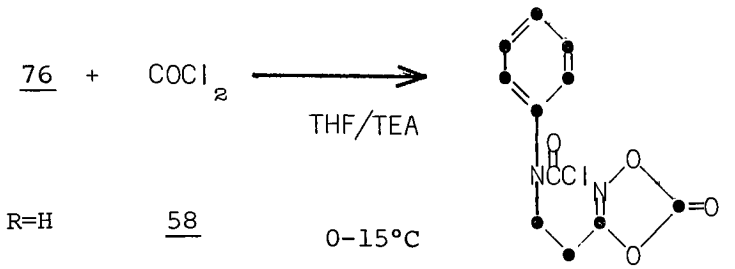
TABLE II

Yields and Properties
of Arylsubstituted Hydroxamic Acids

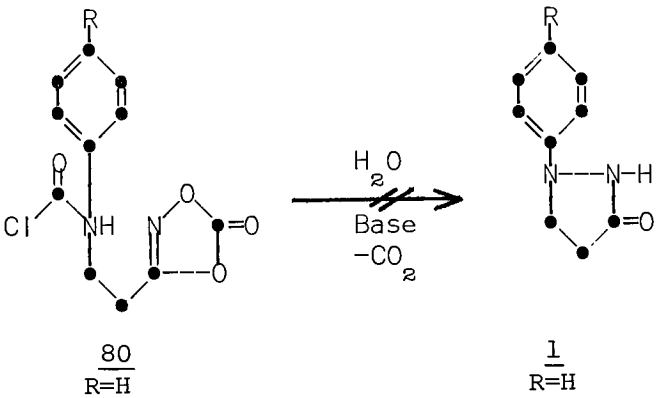


76

R	% Yield	M.P. °C	Elemental Combustion Analysis C:H:N	
			Calculated	Found
H	70	112-115	59.9:6.7:15.5	60.0:6.7:15.5
CH_3	71.3	159-160	61.5:7.6:14.3	61.8:7.3:14.4
OCH_3	60.8	108-110	56.8:6.7:13.5	57.1:6.7:13.7
Cl	58.2	158-160 (hydrochloride)	43.0:4.8:11.2	42.7:4.9:10.8
NO_2	56	170-173	46.8:5.0:17.9	46.8:5.0:17.4

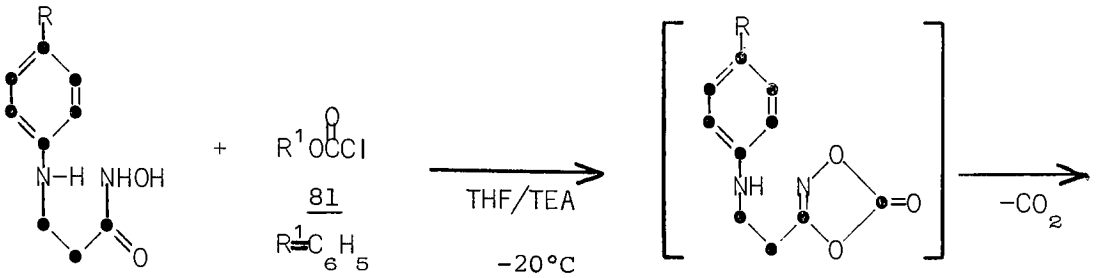


Decomposition of 80 by hydrolysis and treatment with aqueous base, e.g. TEA, Na_2CO_3, was unsuccessful in effecting a possible rearrangement to 1 (R=H). Thermolysis of 80 in boiling xylene showed evidence for isocyanate formation by appearance of the characteristic R-N=C=O band in the IR at 2250 cm^{-1}.



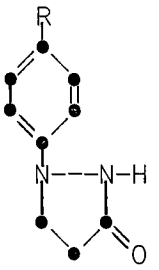
Due to the over-reactivity of phosgene towards the hydroxamic acid, less reactive phosgene substitutes were contemplated. Chloroformates were proposed, and when phenyl chloroformate was substituted for phosgene not only was dioxazolone formed but the desired decomposition of dioxazolone occurred in the following manner (Scheme 3).

Scheme 3



76 (R=H)

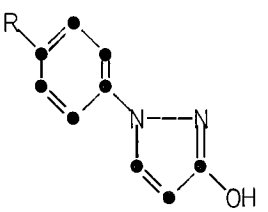
56 (R=H)



1 (R=H)

Phenylchloroformate 83 was added dropwise to a chilled mixture of hydroxamic acid 76 (R=H) and TEA in tetrahydrofuran (THF) followed by gradual warming of the reaction mixture to room temperature. Filtration of TEA-hydrochloride and concentration of solvent resulted in a crude oil which showed signs of gas evolution (CO_2). Dissolving the oil in IPA and allowing the solution to crystallize resulted in a 16% yield of the pyrazolidinone 1 (R=H). A 63% yield of 1 (R=H) was obtained with a slower addition of chloroformate at -40°C to -20°C. TLC analysis of the reaction mixture after addition of the chloroformate showed consumption of the starting

hydroxamic acid and appearance of a new component plus a trace amount of Phenidone 1 (R=H). Allowing the reaction mixture to warm slowly to room temperature caused this new component to disappear with the concomitant formation of Phenidone 1 (R=H) and a minor impurity as indicated by TLC analysis. Furthermore, an aliquot of the cold reaction mixture, taken subsequent to the addition of chloroformate, exhibited a C=O stretching band (1820 cm^{-1} - 1855 cm^{-1}) in the IR representative of dioxazolone formation. The major by-product proved to be the oxidized analog of the pyrazolidinone, 1-phenyl-3-hydroxypyrazole 82 (R=H), by comparison to an authentic sample using TLC and ^{1}H NMR analysis.



82

Other chloroformates were tried in context to our success with phenyl chloroformate for preparation of 1 (R=H).

As noted in Table III, the use of various chloroformates resulted in moderate yields of pyrazolidinone 1 (R=H), except for methyl chloroformate. The use of p-nitrophenyl chloroformate ($R^1=NO_2C_6H_5$) resulted in the highest yield of 1 (R=H); however, the final product was contaminated with p-nitrophenol after isolation. Trichloroethyl chloroformate did seem to reduce the level of 82 (R=H). Reactions

TABLE III

Yields of Pyrazolidinone 1 (R=H) and Imidazolidinone 32 (R=H) Using Various Chloroformates ($R^1OC(=O)-Cl$) in the Hydroxamic Acid to Pyrazolidinone Reaction

R^1	% Yield 1 (R=H)	32 (R=H)
C_6H_5	63	-
$C(Cl)_3CH_2$	62	-
C_2H_5S	53	-
$p\text{-}NO_2C_6H_5$	64	-
CH_3	50 :	50 (mixture)

were run under inert conditions (N_2, Ar) and in the presence of oxidation inhibitors, e.g., diethylhydroxylamine and 2,6-di-tert-butyl-p-cresol (BHT), to help suppress the levels of 82; however, no improvement in yield was seen.

When methyl chloroformate ($R^1=CH_3$) was used in the preparation of the dioxazolone, a low yield of imidazolidinone 32 (R=H) was isolated. ^1H NMR analysis of the crude reaction mixture indicated a 50:50 mixture of pyrazolidinone 1 (R=H) and imidazolidinone 32 (R=H)

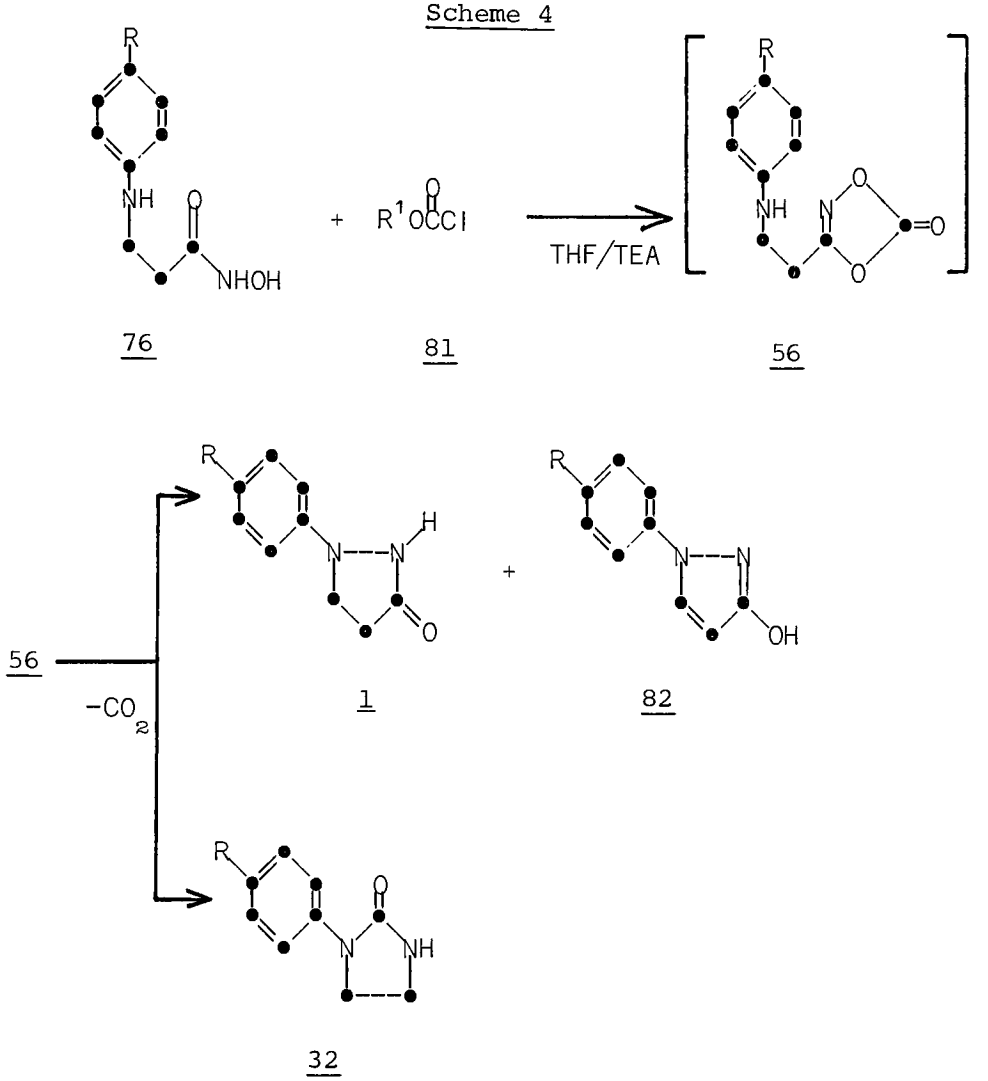
A study using 4'-substituted aryl-3-propiono-hydroxamic acid was investigated with respect to this successful dioxazolone to pyrazolidinone reaction (Scheme 4). These results are summarized in Table IV.

TABLE IV

Yields and Properties of
Substituted Pyrazolidinones 1
and Imidazolidinones 32 from Reaction of
Hydroxamic Acids 78 with Trichloroethyl Chloroformate

R	% 1	% 32	M.P. °C (Lit. M.P. °C)
H	62	-	121-122(121.5-122.5)[33]
CH_3	43	-	157-159(163)[33]
OCH_3	46	-	142-143(146)[34]
Cl	41	-	115-117(117)[35]
NO_2	-	34	243(245)[36]

Scheme 4



76 81 56

1 82

32

R=H, CH_3OCH_3, Cl, NO_2

Generally, moderate yields were obtained using either phenyl chloroformate or trichloroethyl chloroformate. The oxidation product 82 was more apparent in R=CH_3 and R=OCH_3 with phenyl chloroformate as reactant. Trichloroethyl chloroformate seemed to reduce the levels of 82 as evidenced by TLC analysis. In the case

of $R=NO_2$, only imidazolidinone could be isolated. The products were characterized by their spectral properties (including mass spectra where necessary) and by comparison of their melting points with values reported in the literature. A summary of the results for the individual substituents is given in Table IV.

A) $\underline{R=CH_3}$

Initially, phenyl chloroformate was tried to prepare the methyl-substituted pyrazolidinone 1 ($R=CH_3$); however, only a low yield (24%) of the desired compound was isolated. Even with trichloroethyl chloroformate, the oxidized compound 82 ($R=CH_3$) was still evident by TLC. Therefore, isolated yields may not reflect the true extent of the reaction due to difficulty of isolating the pyrazolidinone from a mixture of itself and the oxidized analog 82.

B) $\underline{R=OCH_3}$

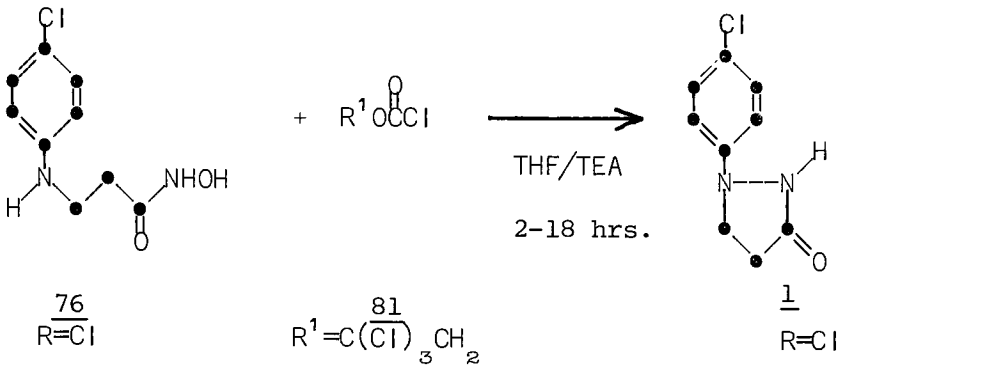
Again phenyl chloroformate was tried to promote the desired reaction with hydroxamic acid 76 ($R=OCH_3$) only to result in 1-(4-methoxyphenyl)-3-hydroxypyrazole 82 ($R=OCH_3$). When trichloroethyl chloroformate was used, a 46% yield of methoxy substituted 1 ($R=OCH_3$) was isolated. HPLC analysis of the reaction mixture before work-up indicated the presence of 85 Area % 1 ($R=OCH_3$). Of special note was the observation 1 ($\dot{R}=OCH_3$) seemed to form faster relative to the previously discussed cases ($R=H, CH_3$). A sample taken immediately after addition of chloroformate was shown by TLC analysis to contain mainly the product 1 ($R=OCH_3$). In contrast, reaction times for 1 ($R=H, CH_3$) were 2-18 hours.

C) R=Cl

Reaction of the hydroxamic acid 76 (R=Cl) with trichloroethyl chloroformate at comparable temperatures (-40°C) resulted in two products, depending on reaction time (Scheme 5).

Scheme 5

a)

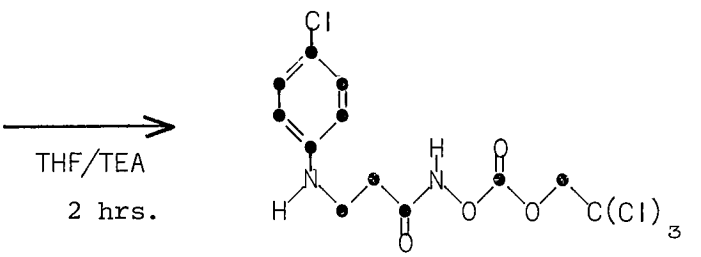


76
R=Cl

81
R¹=C(Cl)₃CH₂

1
R=Cl

b) 76 (R=Cl) + 81 (R¹=C(Cl)₃CH₂)



83

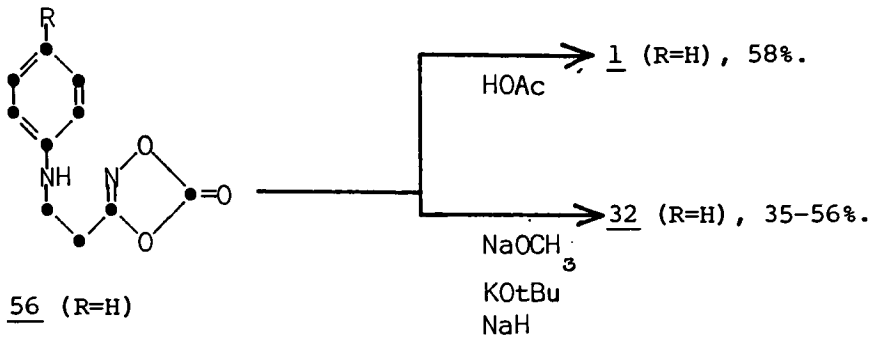
In the first example, illustrated in Scheme 5a, trichloroethyl chloroformate reacted with the hydroxamic acid to form pyrazolidinone 1 (R=Cl) in a similar manner to the previously described examples. As with the other derivatives detailed above, the presence of 1-(4-chlorophenyl)-3-hydroxypyrazole 82 (R=Cl) was also noted by TLC

and confirmed by ^{1}H NMR. An intermediate 83 (Scheme 5b) was isolated from the reaction mixture after 2 hours by filtration of TEA hydrochloride, concentration of THF, and crystallization from ethanol. The intermediate was characterized by ^{1}H, ^{13}C NMR, and IR analysis; however, the compound was too unstable to obtain a suitable mass spectrum. Qualitatively, this intermediate rearranged to pyrazolidinone 1 (R=Cl) by treatment with base (TEA) in THF at room temperature (TLC analysis).

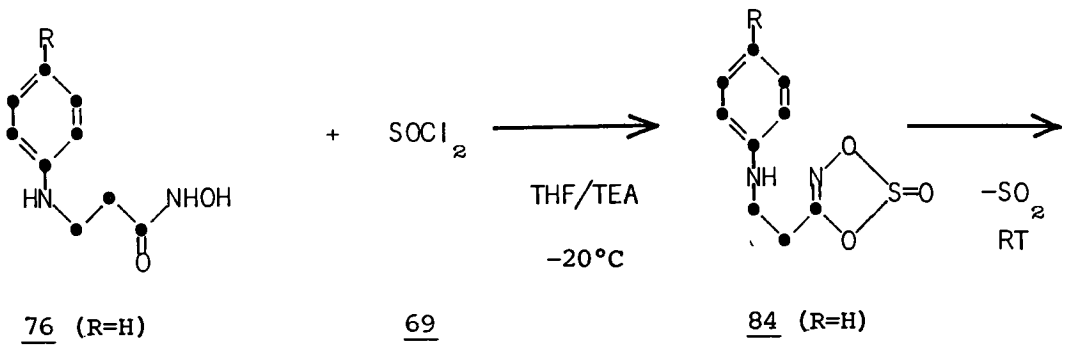
D) R=NO_2

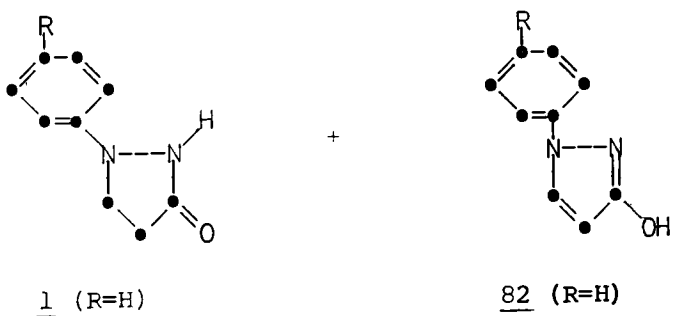
Reaction of the hydroxamic acid 76 (R=NO_2) with trichloroethyl chloroformate was slower relative to the other hydroxamic acids. Warmer reaction temperatures (25°-40°C) or longer stirring periods were necessary to complete the reaction. Contrary to the other examples, a 34% yield of the substituted imidazolidinone 32 (R=NO_2) was isolated. Infared analysis of aliquots of the reaction mixture provided evidence for dioxazolone formation by showing the presence of the characteristic IR bands at 1825 and 1865 cm^{-1}. No evidence for pyrazolidinone 1 (R=NO_2) formation was observed.

The effect of acid and base prior to decomposition of the dioxazolone 56 (R=H) was examined. Added acid (HOAc) did not have a noticeable effect; a yield of 58% of 1 (R=H) was obtained. However, when base ($NaOCH_3$) was added before warming the reaction mixture to room temperature, a rapid temperature increase was observed, and after work-up, a 44% yield of imidazolidinone 32 (R=H) was obtained. This effect was also observed with NaH and KOBut with similar yields (35-43%)



Finally, an attempt was made to prepare the analogous 1,3,2,4-dioxathiazol-S-oxide ring system 84 (R=H) by reaction of 76 (R=H) with thionyl chloride. A 27% yield of 1 (R=H) was obtained but the reaction mixture contained a high level of 82 (R=H) in relation to reactions that utilized chloroformates.

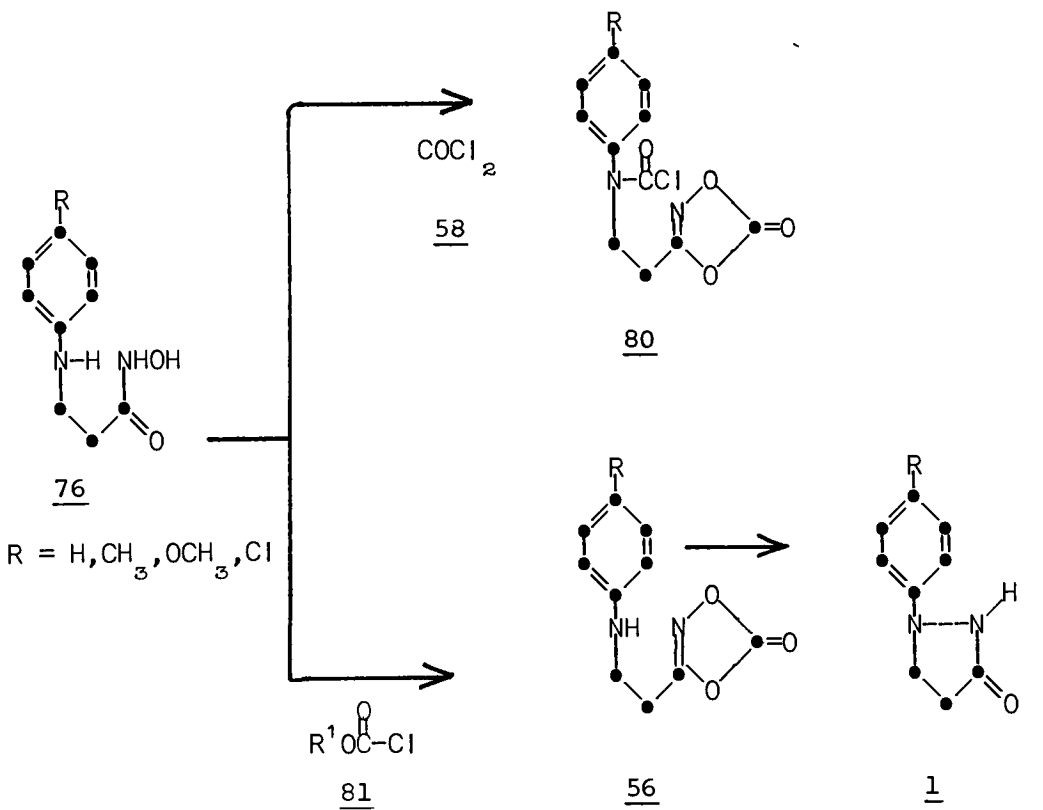




DISCUSSION

Reaction of phosgene 58 with the hydroxamic acid 76 (R=H) results in a nitrogen-blocked dioxazolone 80. This dioxazolone being quite stable (M.P. 67°-68°C) suggests that a free anilino nitrogen is necessary for decomposition to form the pyrazolidinone ring. Attempts to decompose this nitrogen-blocked dioxazolone to 1 by treatment with base or thermolysis were unsuccessful.

The less reactive chloroformates 81 react selectively with the hydroxamic acid functionality of 76 yielding an unstable dioxazolone 56 which under mild conditions decomposes to pyrazolidinone 1.

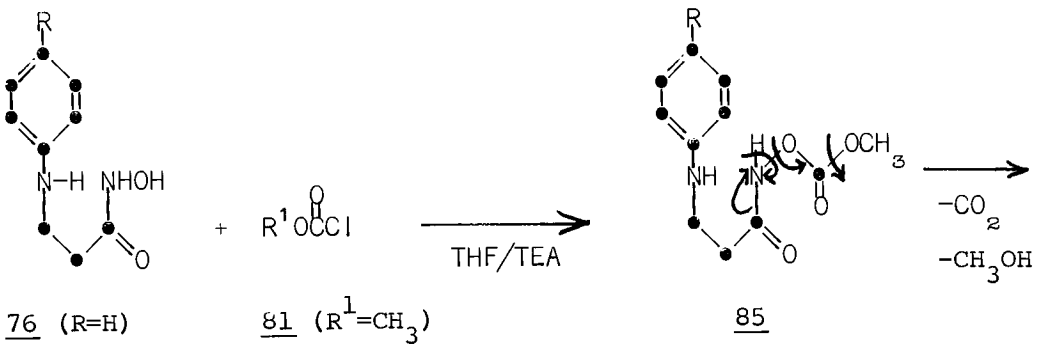


Spectral evidence supports the existence of a dioxazolone precursor; however, actual isolation of 56 was not possible due to its ready decomposition to pyrazolidinone through nitrogen-nitrogen bond formation. Further evidence for the dioxazolone intermediate was supported by tlc examination of the reaction mixtures. Initially, a new component was observed immediately after addition of chloroformate to the hydroxamic acid. Sampling of the reaction mixture at this point and subsequent IR analysis showed the characteristic carbonyl stretch for dioxazolones (1825-1875 cm^{-1}). Eventually, this component disappeared by tlc with appearance of pyrazolidinone. Together these two observations support the existence of an intermediate dioxazolone in the discussed reaction.

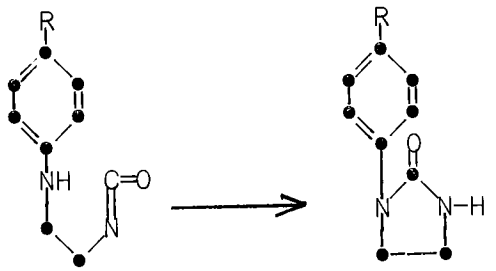
As noted in Table 3, various chloroformates were tried for optimization of the dioxazolone 56 - phenidone 1 (R=H) conversion. Generally, moderate yields resulted regardless of the reagent; however, trichloroethyl chloroformate demonstrated advantages when applied towards reaction with substituted hydroxamic acids 76 (R=CH_3, OCH_3 Cl). The principle advantage was that the oxidized analog of pyrazolidinone 1, 1-phenyl-3-hydroxypyrazole 82, was less apparent relative to 1. Initially, the substituted pyrazolidinones 1 (R=CH_3, OCH_3) were not successfully prepared from the reaction of substituted hydroxamic acids 76 with phenylchloroformate. Mixtures of 1 (R=CH_3, OCH_3), and 82 (R=CH_3 OCH_3), or only the oxidized product 82 were isolated. The use of trichloroethyl chloroformate resulted in more consistent yields of 1 (R=CH_3, OCH_3). We also tried to use p-nitrophenyl chloroformate and ethylthiol chloroformate in the preparation of 1 (R=H). Certain disadvantages were encountered with application

of these two chloroformates. In the first example, the product 1 (R=H) was contaminated with p-nitrophenol. In the latter case, tlc indicated more of the oxidized component 82 and a lower yield of 1 (53%) was obtained.

An alkyl chloroformate was tried in the preparation of pyrazolidinone 1 from hydroxamic acid. The use of methyl chloroformate resulted in mainly imidazolidinone 32. The occurrence of imidazolidinone from addition of methyl chloroformate may be rationalized as follows:



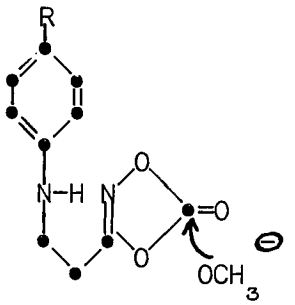
76 (R=H) 81 (R^1=CH_3) 85



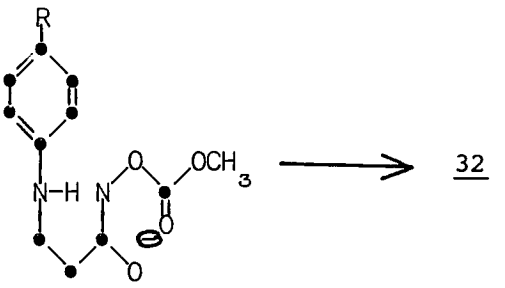
86 32

MeOH is not as good a leaving group relative to phenol or trichloroethanol. This may inhibit dioxazolone formation and lead to a product of a Lossen-type rearrangement. As a result, an intermediate 86 rearranges to the isocyanate-derived imidazolidinone 32.

A related effect was observed when base was added to a cold reaction mixture containing dioxazolone 56 (R=H). Addition of $NaOCH_3$ to the reaction mixture resulted in a temperature increase, and imidazolidinone 32 was isolated from the reaction. $NaOCH_3$ may add to the dioxazolone carbonyl in such a way to effect ring opening, resulting in intermediate 86. Subsequent decomposition of 86, as discussed above, gives rise to imidazolidinone 32.



56



87

However, the use of sodium hydride and potassium t-butoxide resulted in similar yields of imidazolidinone 32 (35-45%). These bases are non-nucleophilic, and particularly sodium hydride would not be expected to open the dioxazolone ring. A more complicated base effect may be operative.

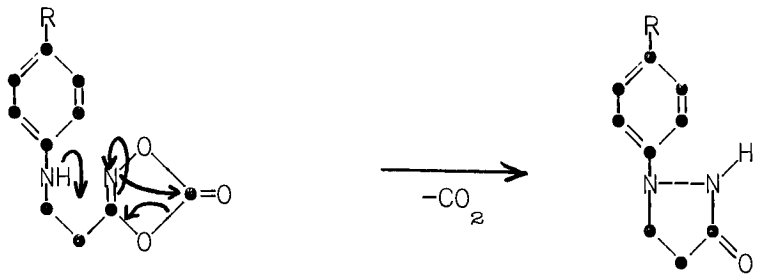
In summary, chloroformates 81 with good leaving groups, e.g., OC_6H_5, $OCH_2C(Cl)_3$, SC_2H_5, $OC_6H_4NO_2$, react with hydroxamic acid to form the desired pyrazolidinone 1. If an alkyl chloroformate such as methyl chloroformate is used, mixtures of pyrazolidinone and imidazolidinone are observed. The oxidized compound 82 is apparent regardless of the chosen chloroformate; however, trichloroethyl chloroformate appears to

be the desired chloroformate for preparing substituted phenidones in moderate yield.

There has been much discussion concerning the oxidized product 82. It appears that oxidation to 82 is internal to the reaction. Inert conditions were employed for running the reaction, as well as anti-oxidants such as BHT and diethyl hydroxylamine, with no effect. Since basic conditions are known for accelerating the oxidation of 1 to 82[2], it can be only presumed that oxidation is related to the basicity of the reaction. Excess TEA is used prior to the addition of chloroformate.

Moderate yields of 4'-substituted pyrazolidinones were obtained when the respective hydroxamic acids were reacted with trichloroethyl chloroformate. These yields, however, may not be truly representative of conversion because mixtures of pyrazolidinone 1 and 1-aryl-3-hydroxypyrazole were formed, causing difficulty in the isolation of pure 1.

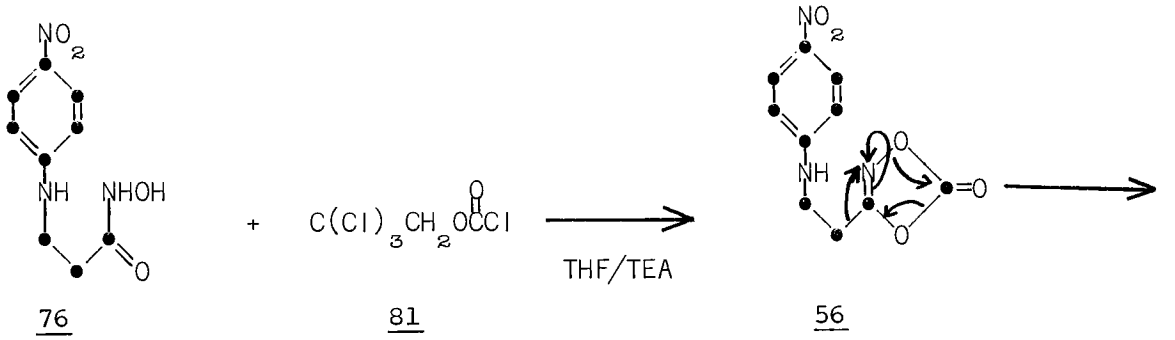
Qualitatively, by tlc analysis, electron-donating substituents R=CH_3, OCH_3 seemed to accelerate the decomposition of dioxazolone 56 to 1. In fact, a very rapid reaction was observed for R=OCH_3. This observation is consistent with a concerted decomposition of dioxazolone 56 since electron-donating substituents would enhance the nucleophilicity of anilino-nitrogen. This would be expected to accelerate the decomposition of dioxazolone to pyrazolidinone as depicted below.



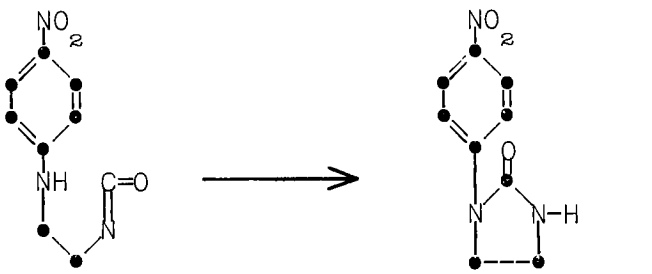
56 1

R = electron donating

Similarly, electron-withdrawing substituents would tend to decrease the nucleophilicity of the anilino-nitrogen, and alkyl migration to electrophilic nitrogen becomes the principle mode of reaction. This possibility was observed for R = NO_2. Low yields of imidazolidinone 32 (R = NO_2) were observed for the dioxazolone reaction. No evidence for pyrazolidinone formation was observed.

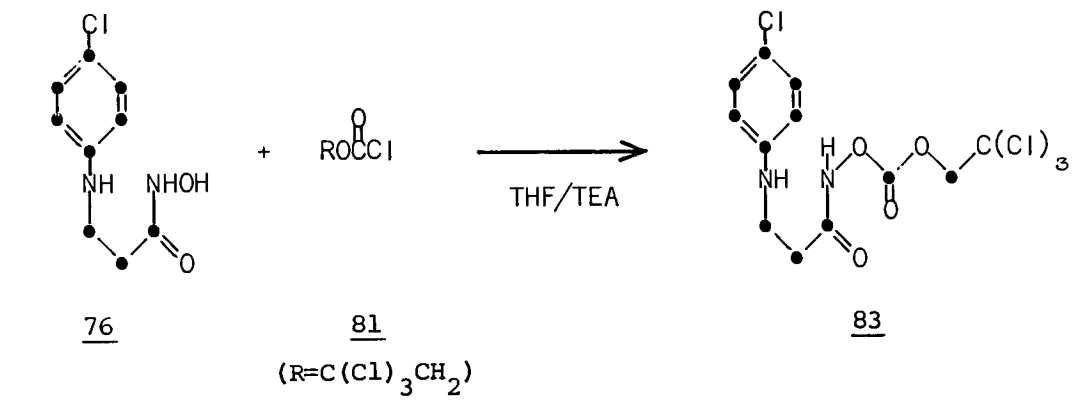


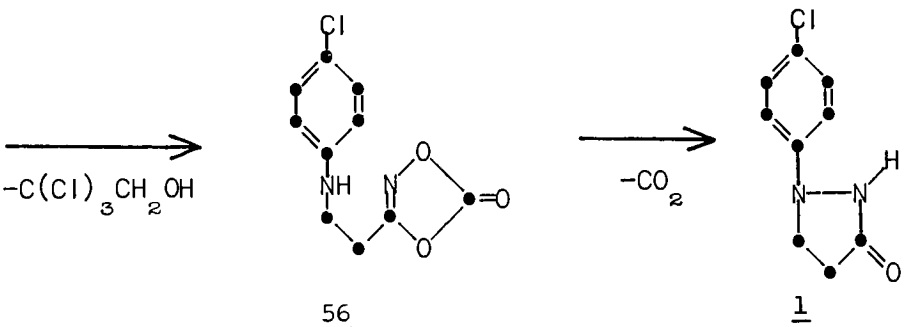
76 81 56



31 32 (R=NO_2)

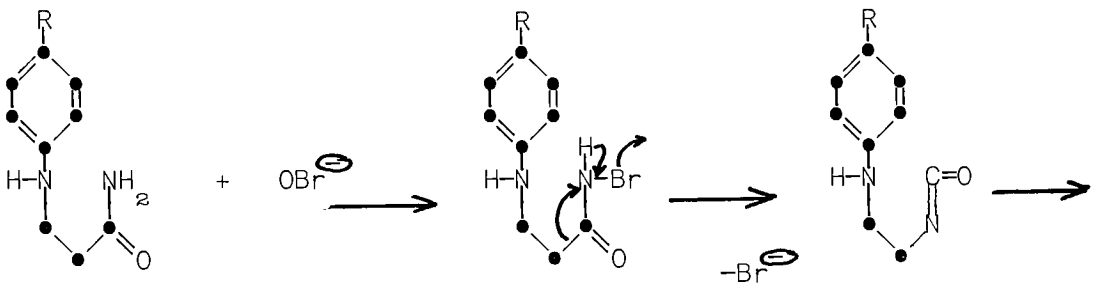
With the weaker electron-withdrawing chloro substituent, a moderate yield of pyrazolidinone was obtained; no imidazolidinone was observed. Interestingly, if the reaction was worked-up two hours after addition of chloroformate, an intermediate 83 was isolated instead of pyrazolidinone. This compound 83 is a stable intermediate before formation of dioxazolone, and when subsequently treated with TEA, it decomposed to pyrazolidinone (tlc analysis). Why such an intermediate in this particular case is stable is unknown.



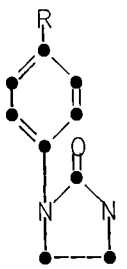


The pyrazolidinones obtained in this work from hydroxamic acids and chloroformates can be contrasted to similar reactions involving electrophilic nitrogen. Reactions such as the Hofmann reaction of

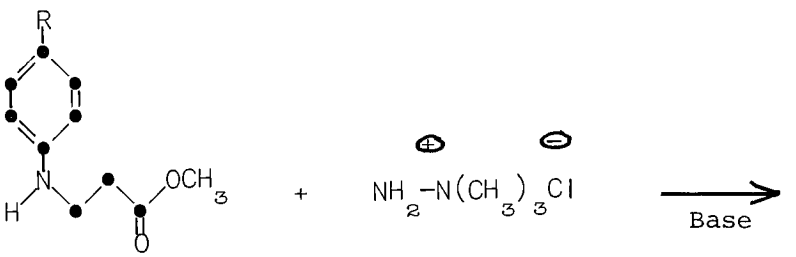
the corresponding amide,[10] along with pyrolysis of amidimides 88 reported by Aelony and McKillip[36], give isocyanate-derived products instead of products representative of N-N bond formation. Alkyl migration to electrophilic nitrogen is the principle mode of reaction, and intermediate isocyanate gave imidazolidinone 32 as the final product.



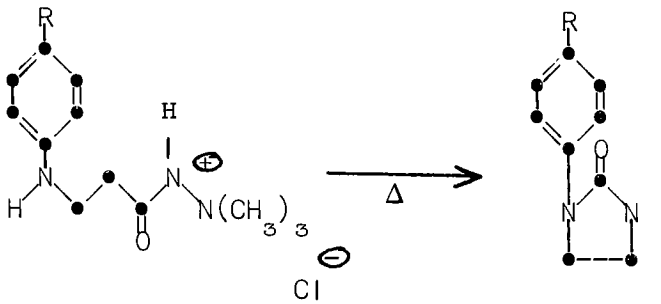
29 30 31



32



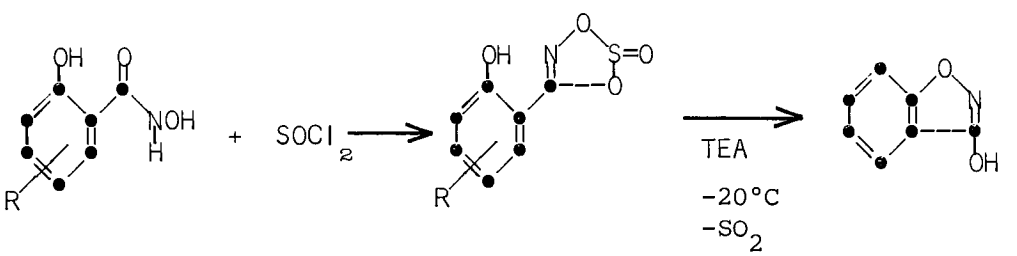
76 88



89 32

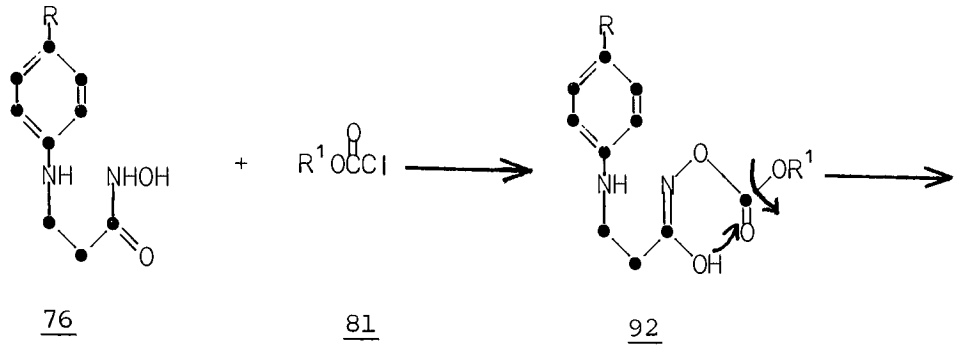
31-90%

The unique feature of our work must be the formation of dioxazolone prior to rearrangement or ring closure. Thus, our work resembles the reaction observed by Boshagen[17] between the salicylic hydroxamic acid 90 and thionyl chloride 91. He found predominately benzisoxazolone (50) formation from the analogous dioxathiazol-S-oxide 52. Heteroatom-induced decomposition of 52 leads to the desired ring system.

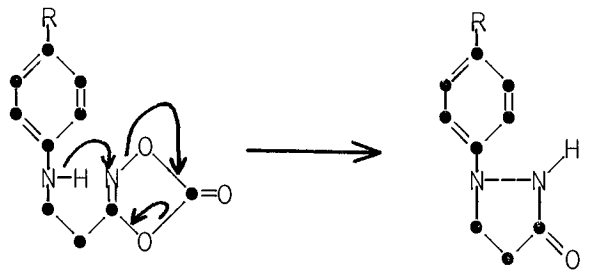


90 91 52 50

Based on the discussed results, we propose the following mechanistic rationalization for the hydroxamic acid to pyrazolidinone conversion. Hydroxamic acid 76 reacts to form dioxazolone 56 which undergoes nitrogen-induced decomposition with simultaneous ring closure to form pyrazolidinone 1.



76 81 92



56 1

Support for this mechanism comes from the previously discussed spectroscopic evidence for dioxazolone formation in conjunction with the mild reaction conditions associated with the rearrangement. When the anilino-nitrogen is blocked as in 80, the dioxazolone is perfectly stable. However, where the nitrogen is unblocked, 56, the dioxazolones are not sufficiently stable to allow isolation. This suggests that this nitrogen plays an important role in the decomposition of dioxazolone as well as its role in ring formation. The study using different aryl substituents also supports this view. Qualitatively, at least, the p-methoxy substituted hydroxamic acid seemed to react faster than the unsubstituted case. Since the p-methoxy substituent increases the basicity of nitrogen, one would expect a more facile ring closure. In contrast, the p-nitro substituent would significantly

reduce the basicity or nucleophilicity of this nitrogen, and indeed, this compound gives no pyrazolidinone. Instead, alkyl migration becomes more favorable and the isocyanate-derived imidazolidinone is the only isolated product.

The existence of aryl-nitrenes has been implicated in the photochemical and thermal decomposition of some dioxazolones[12,14]. The mildness of the decomposition in this work, along with the observed substituent effect, suggests that aryl-nitrenes are not involved in our transformation.

Unfortunately, the mildness of this reaction and the lability of the dioxazolones precluded their isolation and, hence, any quantitative study of substituent effects. However, we have demonstrated a synthetically useful preparation of selectively substituted pyrazolidinones which do not rely on the prior preparation of the corresponding aryl hydrazines.

EXPERIMENTAL

General

Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. Melting points (uncorrected) were obtained in capillary tubes with a Thomas-Hoover apparatus. Boiling points, unless otherwise stated, were read from a thermometer inserted into a distillation head and are uncorrected. IR spectra were obtained from a Perkin-Elmer 599 B infrared spectrophotometer. ^{1}H NMR spectra were obtained at 90 MHz as solutions in the indicated solvent using a Varian EM 390 NMR spectrophotometer. Chemical shifts are expressed in parts per million (δ units) downfield from internal tetramethylsilane (S = singlet, Br = broad singlet, D = doublet, T = triplet, Q = quartet, M = multiplet). ^{13}C NMR spectra were obtained in the indicated solvent with a Varian XL-100 NMR spectrophotometer at 25.2 MHz. Low resolution mass spectra were obtained by electron impact on an Associated Electrical Industries Ltd. A.E.I. MS 902 instrument. Elemental analyses were done by Analytical Services Division, Eastman Kodak Research Laboratories. Thin-layer chromatography was done on EM silica-gel 60 F-254 pre-coated plates and visualized under U.V. light.

Reactions

Methyl 3-Anilinopropionate 74 (R=H)

This compound was prepared from the general procedure of Southwick and Crouch[27]. A solution of 46.5 g (0.499 mole) aniline was added

to 44.8 g (0.52 mole) methyl acrylate, and the mixture was heated to 95°C for 3 hours on a steam bath. The solution was poured into 100 mL H_2O and extracted with 125 mL isopropyl ether. The product was concentrated and distilled under vacuum to yield 70 g (78%) of a yellow oil which solidified: BP 110°-130°C (0.7-1.5 mm) [Lit.[27] BP 139°-146°C (1-2 mm)] MP 37°C; IR (KBr) 3380, 1730 cm^{-1}; ^1H NMR (CCl_4) δ 7.2 (T:2H), 6.5(M:3H), 4.9 (S:1H), 3.6(S:3H), 3.4 (T:2H), 2.5 (T:2H).

Methyl 3-(4-methylanilino)propionate 74 ($R=CH_3$)

The substituted anilinopropionate was prepared according to the modified synthesis by Southwick and Crouch[27] using $SnCl_4$ as catalyst. A mixture of 35.3 g (0.33 mole) p-toluidine, 28.4 g (0.33 mole) methylacrylate, 40 mL toluene, and 10 drops $SnCl_4$ was heated at 75°-80°C for 24 hours. The product was concentrated under vacuum to a crude solid and distilled to yield 29.4 g (46%) of a low-melting white solid: BP 144°-145°C (0.35-0.50 mm) [Lit.[27] BP 145°-146°C (5-6 mm)] IR (KBr) 3200, 1730 cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.1 (D:2H), 6.6 (D:2H), 3.9 (S:1H), 3.65 (S:3H), 3.4 (T:2H), 2.6 (T:2H), 2.2 (S:3H).

Methyl 3-(4-methoxyanilino)propionate 74 ($R=OCH_3$)

A mixture of 98.4 g (0.798 mole) p-ansidine, 80 mL toluene, 24 drops anhydrous $SnCl_4$, and 79.2 g (0.920 mole) methyl acrylate was heated to 85°C for 24 hours. The solution was concentrated under vacuum and distilled to yield 133.7 g (80.1%) of crystalline product: BP 146°-170°C (0.5 mm-1.5 mm) [Lit.[28] BP 143°-152°C (0.65 mm)] MP 53-55°C; IR (KBr) 3360, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.7 (Q:4H), 3.9 (S:1H), 3.7 (S:3H), 3.6 (S:3H), 3.3 (T:2H), 3.5 (T:2H).

Methyl 3-(4-chloroanilino)propionate 74 (R=Cl)

A mixture of 127.5 g (1.0 mole) p-chloroaniline, 191.1 g (2.2 mole) methyl acrylate, and 100 mL HOAc was heated to reflux for 3 hours and concentrated under vacuum to an oil. The brown oil was poured into 1 L H_2O, and a solid crystallized with stirring. The product was collected by filtration and recrystallized with 500 mL of 1:1 CH_3OH:H_2O to yield 129.4 g (60.6%): MP 49°-54°C [Lit.[29] MP 58°-60°C] IR (KBr) 3390, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (M:2H), 6.5 (M:2H), 4.0 (S:1H), 3.7 (S:3H), 3.40 (T:2H), 2.6 (T:2H).

Methyl 3-(4-nitroanilino)propionate 74 ($R=NO_2$)

A mixture of 60.6 g (0.429 mole) 4-nitro-fluorobenzene, 120.0 g (0.859 mole) methyl-3-aminopropionate hydrochloride, 86.9 g (0.859 mole) TEA, and 1200 mL DMSO was heated in a constant temperature bath at 50°C for 48 hours. The solution was added to 8 L cold H_2O, and the resulting yellow slurry was warmed to 22°C and filtered to yield 75.9 g (78%) of a yellow solid: MP 100°-102°C [Lit.[30] MP 102°C] IR (KBr) 3380, 1710 cm^{-1}, ^1H NMR ($CDCl_3$, DMSO-d_6) δ8.15 (D:2H), 6.7 (D:2H), 6.5 (br:1H), 3.75 (S:3H), 3.55 (T:2H), 2.7 (T:2H).

N-Hydroxy-3-anilinopropanamide 76 (R=H)

A mixture of 135.6 g (1.94 mole) hydroxylamine hydrochloride, 348 g (1.94 mL) methyl 3-anilinopropionate 74 (R=H), 960 mL H_2O, and 2,880 mL CH_3OH were combined at room temperature. To the mixture at 13°C was added dropwise 388 mL (3.88 mol) 10 N NaOH. The reaction was warmed to room temperature for 1 hour, and TLC analysis

(4 $CHCl_3$:1 CH_3OH) indicated a lower R_f component and no remaining starting material. The solution was cooled to 13°C and acidified with 334 mL (3.88 mole) concentrated HCl to pH 7; gas evolution was evident. The solution was placed under vacuum overnight. In the morning, the product had precipitated and 1 L of cold H_2O was added. The off-white solid was collected by filtration and washed with isopropyl alcohol (IPA) to yield 243.8 g (70%) of an off-white solid: MP 113°-115°C, IR (KBr) 3340, 1635, 1500, 1745, 745, 690 cm^{-1}; ^1H NMR (acetone-d_6) δ10.4 (S:1H), 7.2 (M:2H), 6.7 (M:3H), 3.4 (T,2H), 2.4 (T,2H); calculated for $C_9H_{12}N_2O_2$ C 59.9; H 6.7; N 15.5 found C 60.0, H 6.7, N 15.5.

N-Hydroxy-3-(4-methylanilino)propanamide 76 (R=CH_3)

To a mixture of 70.0 g (0.36 mole) methyl 3-(4-methylanilino-propionate 74 (R=CH_3) in 585 mL CH_3OH and 182 mL H_2O was added 25.3 g (0.36 mole) hydroxylamine hydrochloride. The reaction mixture was cooled to 10°C and 72 mL (0.72 mole) 10 N NaOH was added dropwise. The slurry went into solution and was stirred at room temperature for 1 hour. To the solution was added dropwise concentrated HCl until a pH of 7 was obtained. This was followed by concentration of solvent under reduced pressure until a slurry resulted. The product was slurried in cold H_2O and collected to yield 49.8 g (71.2%) of an off-white solid: MP 113°-114°C; IR (KBr) 3230, 2860, 1650, 1500, 820 cm^{-1}; ^1H NMR (DMSO-d_6, acetone-d_6) δ 10.5 (Br:H), 7.0 (D:2H), 6.6 (D:2H), 3.3 (T:2H), 2.3 (T, 2H), 2.2 (S:3H); calculated for $C_{10}H_{14}N_2O_2$ C 61.8, H 7.3, N 14.4 found C 61.5, H 7.6, N 14.3.

N-Hydroxy-3-(4-methoxyanilino)propanamide 76 ($R=OCH_3$)

To a mixture of 55 mL H_2O, 175 mL CH_3OH, and 20.9 g (0.1 mole) methyl 3-(4-methoxyanilino)propionate 74 ($R=OCH_3$) was added 7.0 g (0.1 mole) hydroxylamine hydrochloride. At room temperature was added 20 mL (0.2 mole) 10 N NaOH dropwise, and a temperature rise from 22°-35°C was noted. The reaction was stirred for 1 hour and then cooled with tap water. The pH was adjusted to pH 7 with 8.6 mL (0.1 mole) concentrated HCl, and gas evolution was evident. The solution was extracted with 100 mL CH_2Cl_2 and with ice bath cooling, a white solid precipitated from the CH_2Cl_2 extract to yield 12.8 g (60.8%): MP 108°-110°C, IR (KBr) 3300, 1640, 1500, 1230, 825 cm^{-1}; ^1H NMR (CD_3OD) δ 6.8 (M:4H), 5.3 (br:2H), 3.7 (S:3H), 3.4 (T:2H), 2.4 (T:2H), calculated for $C_{10}H_{14}N_2O_3$ C 56.8, H 6.7, N 13.5 found C 57.1, H 6.7, N 13.7.

N-Hydroxy-3-(4-chloroanilino)propanamide Hydrochloride 76 (R=Cl)

To a mixture of 42.7 g (0.2 mole) methyl 3-(4-chloroanilino) propionate 74 (R=Cl), 356 mL CH_3OH, and 110 mL H_2O was added 14.0 g (0.2 mole) hydroxylamine hydrochloride. At 20°C, 40 mL (0.4 mole) 10 N NaOH was added slowly to neutralize hydroxylamine hydrochloride, and a temperature increase to 25°C was seen. The reaction was monitored by TLC analysis (4 $CHCl_3$:1 CH_3OH) which showed a small amount of unreacted 74. The reaction mixture was heated to 40°C for 0.5 hour to complete the reaction. After cooling to room temperature, concentrated HCl was added dropwise to neutralize the product, and concentrated under vacuum to an oil. The oil was extracted with ETOAc, dried over $MgSO_4$, and concentrated under vacuum. The oil was

dissolved in 150 mL THF and with ice bath cooling, anhydrous HCl was passed through the solution which resulted in a precipitate. The slurry was cooled to 0°C and filtered to yield 29.0 g (58.2%) of a white solid: MP 158°-160°C; IR (KBr) 3180, 1635, 1490, 810 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.8 (Br:4H), 7.6 (M:4H), 3.4 (T:2H), 2.5 (T:2H) calculated for $C_9H_{12}Cl_2N_2O_2$ C 43.0, H 4.8, N 11.2 found C 42.7, H 4.9, N 10.8.

N-Hydroxy-3-(4-nitroanilino)propanamide 76 (R=NO_2)

To a suspension of 65.0 g (0.289 mole) methyl 3-(4-nitroanilino) propionate 74 (R=NO_2) in 590 mL CH_3OH and 185 mL H_2O at room temperature was added 22.2 g (0.318 mole) hydroxylamine hydrochloride. The reaction mixture was cooled to 15°C, and 58 mL (0.578 mole) 10 N NaOH was added dropwise. The slurry slowly turned to a turbid solution and a temperature exotherm to 22°C was observed. The reaction was placed in a constant temperature bath (40°C), and 20 mL H_2O was added to effect total solution. After 1 hour, TLC analysis (4 $CHCl_3$: 1 CH_3OH) indicated a new component with a trace of starting material and 25 mL (0.289 mole) concentrated HCl was added to neutralize the excess base. The product precipitated soon afterwards and was collected at room temperature to yield 36.4 g (56.0%) of a yellow solid: MP 170°-173°C; IR (KBr) 3400, 1590, 1280 cm^{-1}, ^1H NMR (DMSO-d_6) δ 10.8 (Br:1H) 8.2 (D:2H), 7.5 (T:1H), 7.8 (D:2H), 3.5 (M:2H), 2.4 (T:2H) calculated for $C_9H_{11}N_3O_4$ C 46.8, H 5.0, N 17.9 found C 46.8, H 5.0, N 17.4.

N-[2-(5-Oxo-1,4,2-dioxazol-3-yl)ethyl]-N-phenylcarbamoyl Chloride 80

To a solution of 5.0 g (0.0278 mole) 76 (R=H), 30 mL THF, and 2.8 g (0.0277 mole) TEA at 0°C was added excess phosgene over 10 minutes;

a temperature increase to 14°C was observed. TLC analyses (4 $CHCl_3$:1 CH_3OH) indicated a new component with no starting material remaining. The salts were filtered off, and the filtrate was concentrated under vacuum to an oil which crystallized upon standing. The solid was slurried in 25 mL IPA and collected to yield 3.1 g (41.6%) of a white solid: MP 67°-68°C, IR (KBr) 1865, 1825, 1715, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5 (M:5H), 4.2 (T:2H), 3.0 (T:2H); m/e = 268 (21%), base ion CO_2; calculated for $C_{11}H_9ClN_2O_4$ C 49.0, H 3.6, N 10.4 found C 49.2, H 3.4, N 10.4.

Attempted Decomposition of 80 to 1-phenyl-3-pyrazolidinone 1

A solution of 0.2 g (0.07 mmol) 80 in 10 mL xylene was heated to reflux for 3 hours and concentrated to an oil: IR (neat) 2900, 2250, 1825, 1870, 1720 cm^{-1}. The single band at 2250 cm^{-1} indicated isocyanate formation. ^1H NMR ($CDCl_3$) showed unreacted starting material 80 δ 4.1 (T:2H), 2.9 (T:2H), and two new methylene absorptions, δ 3.4 (T:2H), 2.3 (T:2H), due to probable isocyanate formation.

1-Phenyl-3-pyrazolidinone 1 (R=H) using Phenyl Chloroformate

A solution of 1.8 g (0.01 mole) 76 (R=H), 10 mL THF, and 1.0 g (0.011 mole) TEA was cooled to -5°C under N_2. At -5°C, 1.7 g (0.11 mole) phenyl chloroformate was added dropwise, and a temperature exotherm to 5°C was observed. TLC analysis (4 $CHCl_3$:1 CH_3OH) indicated a new component and a minor component with no starting material. After 1 hour, the salts were filtered, and the filtrate was concentrated to an oil. Gas evolution (CO_2) was evident and after crystallization of the oil

in IPA, 0.3 g (16.1%) of a pink solid 1 (R=H) was isolated: MP 115°-116°C [Lit.[33] MP 121.5°-122.5°C] IR (KBr) 2840, 1675, 1590, 745 cm^{-1}, ^1H NMR ($CDCl_3$) δ 9.8 (Br:1H), 7.4 (M:2H), 7.2 (M:3H), 3.9 (T:2H), 2.6 (T:2H), IR and ^1H NMR spectra were identical to an authentic sample of 1, m/e = 162, calculated for $C_9H_{10}N_2O$.

1-Phenyl-3-pyrazolidinone 1 (R=H) using Phenyl Chloroformate

To a solution of 10.0 g (0.055 mole) 76 (R=H) in 100 mL THF under N_2 was added 6.2 g (0.061 mole) TEA at -20°C. With continued cooling was added 9.6 g (0.061 mole) phenyl chloroformate 83 ($R=C_6H_5$) over 10 minutes. A temperature exotherm to -5°C occurred with formation of TEA hydrochloride salts. TLC analysis (60 $CHCl_3$:30 toluene:10 HOAc) indicated consumption of starting material and the formation of an upper R_f component, presumably the dioxazolone 56 (R=H). An IR spectrum of the reaction mixture showed the characteristic dioxazolone bands (1820, 1865 cm^{-1}). The mixture was allowed to warm to room temperature, and salts were filtered off. The filtrate was concentrated under vacuum at 30°C. The residue solidified upon standing and gas evolution was apparent. TLC analysis now indicated a component with the R_f of 1 and a minor impurity associated with 82 (R=H). To the solid was added 25 mL IPA, and the mixture was stirred overnight. After filtration, 5.6 g (63%) of 1 (R=H) was obtained: IR and ^1H NMR spectra were identical to an authentic sample of 1.

1-Phenyl-3-pyrazolidinone 1 (R=H) using Trichloroethyl Chloroformate

A solution of 10.0 g (0.055 mole) 76 (R=H), 100 mL THF, and 5.6 g (0.055 mole) TEA was cooled to -20°C under N_2 and 12.2 g (0.057 mole) trichloroethyl chloroformate was added dropwise with a temperature increase to -10°C. The reaction mixture was allowed to warm to room temperature overnight. In the morning, TLC analysis (60 $CHCl_3$:30 toluene: 10 HOAc) indicated a major component consistent with Phenidone and a minor component indicative of 82 (R=H). The salts were filtered, and the filtrate concentrated under vacuum to an oil. The product was crystallized using 20 mL IPA and collected at 0°C to yield 5.5 g (62%) 1 (R=H): MP 121°-122°C.

1-Phenyl-3-pyrazolidinone 1 (R=H) using Ethyl Chlorothiolformate

A solution of 3.6 g (0.02 mole) 76 (R=H), 40 mL THF, and 2.0 g (0.02 mole) TEA was cooled to -30°C. At -30°C, 2.5 g (0.02 mole) ethyl chlorothiolformate 81 (R^1=SC_2H_5) was added dropwise, and the reaction mixture was allowed to warm to room temperature overnight. In the morning, the salts were filtered and the filtrate was concentrated to an oil. The oil was dissolved in 10 mL IPA and quickly crystallized to yield 1.7 g (53%) 1.

1-Phenyl-3-pyrazolidinone 1 (R=H) using p-nitrophenyl Chloroformate

To a solution of 10.0 g (0.055 mole) 76 R=H), 100 mL THF, and 5.6 g (0.055 mole) TEA under N_2 was added portionwise 11.1 g (0.055 mole) p-nitrophenyl chloroformate 81 (R^1=p-$NO_2C_6H_5$). The reaction mixture was allowed to warm to room temperature overnight. In the morning, salts were filtered, and the filtrate was concentrated to an oil. After crystallization from IPA, a 64% yield of 1 (R=H) was recovered with a minor impurity of p-nitrophenol, as indicated by ^1H NMR analysis.

1-Phenyl-3-pyrazolidinone 1 (R=H) and 1-phenyl-2-imidazolidinone 32 (R=H) by Reaction of 76 (R=H) with Methyl Chloroformate

A solution of 10.0 g (0.055 mole) 76 (R=H), 100 mL THF, and 6.2 g (0.061 mole) TEA was cooled to -5°C under N_2. At -5°C, a solution of 5.2 g (0.061 mole) methyl chloroformate 81 ($R=CH_3$) was added dropwise and a temperature increase to 5°C was observed. The reaction mixture was allowed to warm to room temperature, and the salts were removed by filtration. The filtrate was reduced to an oil under vacuum. ^1H NMR analysis indicated a 50:50 mixture of 1 (R=H) and 32 (R=H) by comparison to spectra obtained from authentic samples of 1 and 32.

1-(4-Methylphenyl)-3-pyrazolidinone 1 ($R=CH_3$) using Phenyl Chloroformate

To a slurry of 3.9 g (0.02 mole) 76($R=CH_3$), 40 mL THF, and 2.0 g (0.02 mole) TEA under N_2 was added 0.3 g (0.002 mole) BHT as antioxidant. The mixture was cooled to -5°C and added dropwise 3.1 g (0.022 mole) phenyl chloroformate 81 ($R^1=C_6H_5$). TLC analysis indicated no reaction, 2.0 g (0.02 mole) additional TEA was added at room temperature and a reaction exotherm to 35°C was observed, and after 1 hour TLC analysis (60 $CHCl_3$:30 toluene:10 HOAc) showed a major component consistent to 1 ($R=CH_3$) as well as a minor impurity of 82 ($R=CH_3$). The salts were filtered, and the filtrate was concentrated under vacuum to an oil which solidified upon standing. The oil was dissolved in 4 mL ethanol and crystallized to yield 0.7 g (24.1%) of a pink solid: MP 157°-159°C [Lit.[33] MP 163°C]; IR (KBr) 3000, 1680, 1275, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ9.5 (br;1 H), 7.1 (M:5H), 3.8 (T:2H), 2.5 (T:2H), 2.3 (S:3H). IR and ^1H NMR spectra were comparable to spectra obtained from an authentic sample of 1 ($R=CH_3$); m/e = 177, calculated for $C_{10}H_{12}N_2O$.

1-(4-Methylphenyl-3-pyrazolidinone 1 ($R=CH_3$) using Trichloroethyl Chloroformate

To a slurry of 10.0 g (0.051 mole) 76 ($R=CH_3$), 100 mL THF, and 5.2 g (0.051 mole) TEA under N_2 was added dropwise 11.1 g (0.0525 mole) trichloroethyl chloroformate. The reaction mixture turned to a heavy slurry and was allowed to warm to room temperature. After stirring overnight, TLC analysis (60 $CHCl_3$:30 toluene:10 HOAc) indicated a major component of 1 ($R=CH_3$) and an upper component indicative of the oxidized product 82 ($R=CH_3$). The salts were removed by filtration, and the filtrate was concentrated to an oil under vacuum. The oil was dissolved in 50 mL ethanol with heat and allowed to crystallize to yield 3.9 g (43%) 1 ($R=CH_3$).

1-(4-Methoxyphenyl)-3-hydroxypyrazole 82 ($R=OCH_3$) using Phenyl Chloroformate

To a slurry of 8.4 g (0.04 mole) 76 ($R=OCH_3$), 84 mL THF, and 4.1 g (0.04 mole) TEA was added dropwise 6.3 g (0.04 mole) phenyl chloroformate keeping the temperature less than -10°C. Immediately after the addition of the chloroformate, TLC analysis indicated the formation of the desired pyrazolidinone 1 ($R=OCH_3$) and a minor upper R_f component. The salts were filtered, and the filtrate was concentrated to an oil under vacuum. The oil was dissolved in 75 mL CH_2Cl_2 and washed with H_2O followed by 1% aqueous $NaHSO_3$. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in 30 mL N-butanol and allowed to crystallize. A small amount of 82 ($R=OCH_3$) 1.9 g (14.5%) was recovered; IR (KBr) 1550, 1500, 1260, 825, ^1H NMR δ10.2 (Br:1H), 7.6 (M:3H), 6.9 (M:2H), 5.8 (D:1H), 3.8 (S:3H). IR and ^1H NMR spectra were identical to spectra obtained from an authentic sample of 82 ($R=OCH_3$).

1-(4-Methoxyphenyl)-3-pyrazolidinone 1 R=(4-$OCH_3C_6H_5$) using Trichloroethyl Chloroformate

A mixture of 7.3 g (0.035 mole) 76 (R=OCH_3), 100 mL THF, and 7.1 g (0.70 mole) TEA under N_2 was stirred and cooled to -40°C. At -40°C was added dropwise 8.5 g (0.040 mL) trichloroethyl chloroformate. The reaction mixture was allowed to warm to room temperature. TLC analysis (60 $CHCl_3$:30 toluene:10 HOAc), immediately after the chloroformate addition, indicated a major component consistent to 1 (R=OCH_3) and a minor component associated with 82 (R=OCH_3). The salts were filtered, and the filtrate was concentrated to an oil. The oil was dissolved in 25 mL ethanol and placed in the refrigerator overnight to crystallize. After filtration, 3.1 g (46%) of a pink solid was isolated consistent in structure to substituted pyrazolidinone 1 (R=OCH_3): MP 146°C; [Lit.[33] MP 146°C] IR (KBr) 3000, 2850, 1690, 1505; ^1H NMR ($CDCl_3$), δ 9.0 (Br:1H), 6.9 (M:4H), 3.75 (M:5H), 2.5 (T:2H).

1-(4-Chlorophenyl)-3-pyrazolidinone 1 (R=Cl)

To a cooled (-40°C) slurry of 5.0 g (0.02 mole) 76 (R=Cl), 50 mL THF, and 4.0 g (0.04 mole) TEA under N_2 was added dropwise, 4.5 g (0.02 mole) trichloroethyl chloroformate in 10 mL THF over a five minute period. A temperature exotherm to -10°C occurred, and the reaction was allowed to warm to room temperature and stirred overnight. TLC analysis (60 $CHCl_3$:30 toluene:10 HOAc) indicated two new components, and the salts were removed by filtration. The filtrate was concentrated to an oil and dissolved in 5 mL ethanol. The product crystallized in two hours and was collected at 5°C to yield 1.6 g

(41%) of a white solid: MP 117°C [Lit.[34] MP 117°C] IR (KBr) 3025, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ10.0 (Br:1H), 7.25 (M:2H), 7.0 (M:2H), 3.85 (T:2H), 2.65 (T:24).

N-[(2,2,2-trichloroethoxy)carbonyloxy]-3-(4-chloroanilino)propanamide 83

A slurry of 5.0 g (0.02 mole) 76 (R=Cl), 50 mL THF, and 4.0 g (0.04 mole) TEA was treated with 4.5 g (0.021 mole) trichloroethyl chloroformate by dropwise addition at -40°C. The mixture was warmed to room temperature (1 hour) and the salts were collected. The filtrate was concentrated to an oil and crystallized from 5 mL ethanol to yield 2.0 g (27%) 83: MP 148°-150°C; IR (KBr) 1800, 1710, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, DMSO-d_6) δ8.75 (M:4H), 5.0 (S:2H), 3.5 (T:2H), 2.8 (T:2H); ^{13}C NMR (DMSO-d_6) δ167.5 (hydroxamic acid C=O), 152.7 (carbonate C=O), 140.4, 129.1, 126.8, 119.6, 94.1, 76.8, 42.6, 29.7. Apparently due to instability, neither a suitable mass spectrum (including chemical ionization), nor a suitable elemental analysis could be obtained).

Reaction of 83 with TEA

A solution of 1.0 g (2.6 mmol) 83 in 10 mL THF and 0.03 g (0.26 mmol) TEA was stirred at room temperature (18 hours). In the morning, TLC analysis (60 $CHCl_3$:30 toluene:10 HOAc) indicated conversion to 1 (R=Cl) with starting 83 still present.

1-(4-Nitrophenyl)-2-imidazolidinone 32 ($R=NO_2$)

To a slurry of 2.25 g (0.01 mole) 76 ($R=NO_2$), 25 mL THF, and 2.0 g (0.02 mole) TEA under N_2 at -40°C was added 2.3 g (0.011 mole) trichloroethyl chloroformate dropwise, and the slurry was allowed to stir overnight, warming to room temperature. In the morning, TLC analysis

indicated a major component and a trace amount of starting 76. The salts were filtered, and the oil concentrated to a residue under vacuum. The residue was slurried in ethanol and filtered to yield 0.7 g (32.5 %) of a tan solid: MP 243°-244°C [Lit.[35] MP 245°C] IR 3250, 1700, 1500, 1320, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$DMSO-d_6) δ 8.2 (D:2H), 7.8 (D:2H), 7.4 (Br:1H), 4.0 (T:2H), 3.6 (T:2H). Note: An IR spectrum was obtained after addition of the chloroformate to the reaction mixture. The characteristic C=O bands for dioxazolones (1825, 1865 cm^{-1}) were observed.

1-Phenyl-2-imidazolidinone 32 (R=H). Treatment of Dioxazolone Mixture with $NaOCH_3$

A solution of 10.0 g (0.055 mole) 76 (R=H), 100 mL THF, and 5.6 g (0.055 mole) TEA was cooled to -40°C. At -40°C, a THF solution of 8.6 g (0.055 mole) phenyl chloroformate was added with a temperature increase to -20°C. The reaction mixture was stirred at -20°C for 0.5 hour, and the slurry was filtered to remove salts. The solution was kept cold (0°C) and 3.0 g (0.055 mole) $NaOCH_3$ was added in one portion to the dioxazolone 56 (R=H); a rapid temperature increase resulted, and TLC analysis of the reaction mixture indicated two components representative of 1 and 32. The reaction mixture was acidified with HCl to pH 6, and the filtrate was concentrated to an oil. The oil crystallized upon standing, and the solid was slurried in ethanol to yield 5.0 g (56%) 32 (R=H): MP 161°-164°C [Lit.[36] MP 165°C); IR (KBr) 3250, 1680, 1480, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.5 (M:4H), 7.2 (M:1H), 6.1 (Br:1H), 3.8 (T:2H), 3.6 (T:2H). Similar results were obtained with sodium hydride and potassium tert-butoxide.

1-Phenyl-3-pyrazolidinone 1 (R=H) using Thionyl Chloride

To a cooled solution (-40°C) under N_2 containing 5.0 g (0.0277 mole) 76 (R=H) in 50 mL THF and 2.8 g (0.0277 mole) TEA was added 3.6 g (0.030 mole) thionyl chloride dropwise to form the substituted 1,3,2,4-dioxathiazole-S-oxide 84 (R=H). The reaction was allowed to warm to room temperature, and the salts were filtered. A TLC sample taken from the filtrate showed two components representative of 1 (R=H) and 82 (R=H). After concentration of solvent, 1.2 g (27%) of 1 (R=H) as an off-white solid was obtained. IR and NMR were identical to an authentic sample.

REFERENCES

1. a) Wiley R. H.; Wiley P., "Pyrazolones, Pyrazolidinones and Derivatives, Part I", Weissberger A. Ed., (1964), Interscience Publishers, New York, Chapter 5, 116

   b) Lieser T.; Kemmer K., Chem. Ber., (1954), 84, 4

2. For a review on photographic developers and Phenidone see "The Theory of the Photographic Process", James T. H. Ed., (1977), McMillan Publishing Co., Inc., Chapter 11, 291

3. a) Stodola F. H., J. Org. Chem., (1948), 13, 757

   b) Rondestvedt C. S.; Chang P. K., J. Am. Chem. Soc., (1955), 77, 6532

   c) Kendall J. D.; Duffin G. F., U. S. Patent, 2, 704, 762 (1955); Chem. Abstr. (1956), 50, 2680f

   d) Spasov Kurtev, Annuaire univ. Sofia, Faculte phys-math, (1946-7), 43 Liure 2, 37; Chem. Abstr., (1950), 44 1491d

4. Kendall J. D.; Duffin G. F.; Axford A. J., U. S. Patent 2, 688, 024 (1954), Chem. Abstr., (1955), 49, 85i

5. Cornforth J. W., "The Chemistry of Penicillin", (1949), 688; cf. Reference 1

6. Lederer L., J. Prakt. Chem., (1892), 45 [2], 83

7. Simonova, N. I., Tr. Leningr. Inst. Kinoinzhenerov, (1961), 6, 19; Chem. Abstr., (1964), 60, 4127a

8. Wulfman D. S., "The Chemistry of Diazonium and Diazo Groups, Patai, S. Ed., (1978), John Wiley and Sons, 247

9. Allen C.; Byers J., U. S. Patent, (1956) 2, 772, 282; Chem. Abstr. (1957), 51, 333d.

10. Rodinov V. M.; Kiseleva U. V., Izert. Akad. Nauk S.S.S.R, Otdel. Khim. Nauk, (1951), 57; Chem. Abstr. (1952), 46, 466i

11. a) Linke S.; Tisue G. T.; Lwowski W., J. Am. Chem. Soc., (1967), 89, 6308

b) Wolff H., Org. React., (1946), 3, 307

c) Smith P. A. S., "Molecular Rearrangements", de Mayo, P. Ed., (1963), 1, Interscience, New York, NY, 507

d) Lwowski W., Angew. Chem. Int. Ed. Engl., (1967), 6, 897

12. Sauer J.; Mayer K. K., Tetrahedron Lett., (1968), 319

13. a) Burk E.; Carlos D., J. Het. Chem., (1970), 7, 177

b) Kaufman W. J., J. Org. Chem., (1974), 39, 2472

c) Hocker J.; Merten R., Ger. Offen. 2, 158, 740 (1973); Chem. Abstr., (1973), 79, 42, 507

d) Naarmann H.; Pohlemann H., Makromal. Chem., (1975), Suppl. I, 74

e) Wohlgemuth L. G.; Fritock W. H., U. S. Patent 3, 647, 760 (1972); Chem. Abstr., (1972), 76, 155, 756

14. Sauer J.; Mayer K. K., Tetrahedron Lett., (1968), 319

15. Eibler E.; Sauer J., Tetrahedron Lett., (1974), 2565

16. Lwowski W., Angew. Chem. Int. Ed. Engl., (1967), 6, 897

17. Böshagen H., Chem. Ber., (1967), 100, 954

18. ibid

19. ibid

20. ibid

21. Korbonitz D.; Bak'o E. M.; Korvath K., J. Chem. Res., (1979), (n), 810

22. Beck G., Chem. Ber., (1951), 84, 689

23. a) Geffken D., Ann., (1982), 211

b) Friary R.; Sunday B. R., J. Het. Chem., (1979), 16, 1277

24. Burk E. H.; Carlos D. D., J. Het. Chem., (1970), 7, 177

25. ibid

26. Kazuho H.; Eisuke k.; Shonosuke Z., Chem. Pharm. Bull. (1980), 28, (11), 3296

27. Southwick P. L.; Crouch R. T., J. Am. Chem. Soc., (1953), 75, 3413

28. Johnson W. S.; Woroch E. L., J. Am. Chem. Soc., (1949), 71, 1901

29. Southwick P. l.; Madhav R.; Fitzgerald J. A., J. Het. Chem., (1969), 6, 507

30. Suhr H., Ann., (1965), 687, 175

31. Biggs D. F.; Coutts R. T.; Selley M. L.; Towill G. A., J. Pharm. Sci., (1972), 61, (11), 1739

32. Sauer J.; Mayer K. K., Tetrahedron Lett., (1968), 318

33. Kendall J. D., Brit. Patent, (1951), 650, 911; Chem. Abstr., (1952), 46, 144

34. Kendall J. D.; Duffin G. W., U. S. Patent, 2, 704, 762, (1955); Chem. Abstr., (1956), 50 2680h

35. Duffin G. F.; Kendall J. D., J. Chem. Soc., (1954), 408

36. Najer H.; Giudicelli R.; Menim J.; Morel C., Compt. Rend., (1961), 253, 2369, Chem. Abstr., (1962), 56, 14256d

37. Aelony D.; McKillip W. J., J. Het. Chem., (1972), 9, 687

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